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UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
- - -  
NONPRESCRIPTION DRUGS ADVISORY COMMITTEE  
- - -  
MEETING  
- - -  
WEDNESDAY, JULY 29, 1998

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1998  
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The Advisory Committee met in Versailles Rooms I and II, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:30 a.m., Eric Brass, M.D., PhD, Acting Chair, presiding.

PRESENT:

ERIC P. BRASS, MD, PhD, Acting Chair  
RHONDA STOVER, R.Ph, Executive Secretary  
MARY A. KODA-KIMBLE, PharmD, Member  
LYNN MCKINLEY-GRANT, MD, Member  
GEORGE A. BLEWITT, MD, Industry Representative  
MARIAN MELISH, MD, Anti-Infective Representative  
ROSELYN RICE, MD, Anti-Infective Representative  
RALPH B. D'AGOSTINO, PhD, SGE, Consultant  
THEODORE G. TONG, PharmD, Consultant  
EDWIN E. GILLIAM, MSN, PhD, CFNP, Guest  
JOHN P. GUZEWICH, MPH, Guest

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PRESENT: (continued)

EDWARD P. KRENZELOK, Pharm D, Guest  
ELAINE L. LARSON, PhD, RN, FAAN, Guest  
DENNIS G. MAKI, MD, Guest  
RICHARD A. NEILL, MD, Guest

LINDA KATZ, MD, MPH, FDA Representative  
DEBBIE LUMPKINS, BS, FDA Representative

Public Comment:

PAUL MARSHALL  
SYED A. SATTAR, PhD  
ABDUL B. ZAFAR, MBBS, MPH

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## P R O C E E D I N G S

Time: 8:31 a.m.

CHAIRMAN BRASS: Thank you and good morning. On behalf of the Nonprescription Drugs Advisory Committee, I'm Eric Brass, and I'll be chairing this morning's meeting.

I'd like to turn the microphone over to Rhonda Stover for the conflict of interest statement.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

With respect to invited guests, there are reported interests with respect to the firms that make health care antiseptics drug products that we believe

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1 should be made public to allow the participants to  
2 objectively evaluate their comments.

3 Dr. Edward P. Krenzelok would like to  
4 disclose that he is the Director of the Pittsburgh  
5 Poison Center. The Center responds to poisoning and  
6 medical emergency inquiries as the corporate poison  
7 center for Colgate U.S. and its subsidiaries.

8 Dr. Elaine Larson would like to disclose  
9 that she is an investigator on 3M Corporation's study  
10 of skin flora and surgical scrubs.

11 Dr. Dennis Maki would like to disclose  
12 that he has grants from Becton-Dickinson/Deseret and  
13 3M Company.

14 In the event that the discussions involve  
15 any other products or firms not already on the agenda  
16 for which an FDA participant has a financial interest,  
17 the participants are aware of the need to exclude  
18 themselves from such involvement, and their exclusion  
19 will be noted for the record.

20 With respect to all other participants, we  
21 ask in the interest of fairness that they address any  
22 current or previous financial involvement with any

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1 firm whose products they may wish to comment upon.

2 Thank you.

3 CHAIRMAN BRASS: We have an unusual  
4 composition at the front table this morning, and  
5 perhaps we can go around the room and introduce this  
6 morning's participants. I'll remind everybody, both  
7 at the table and other speakers, to please always use  
8 the microphones, and bring the microphone close to ,  
9 your mouth when talking, so that the transcriptionist  
10 can capture all your contributions.

11 We can start at the end of the table.

12 DR. NEILL: My name is Richard Neill. I'm  
13 a family physician and faculty member at the  
14 University of Pennsylvania in the Department of Family  
15 Practice and Community Medicine.

16 DR. KRENZELOK: I'm Ed Krenzelok. I'm  
17 Director of the Pittsburgh Poison Center. I'm a  
18 professor of pharmacy and pediatrics at the University  
19 of Pittsburgh, and currently President of the American  
20 Academy of Clinical Toxicology.

21 DR. GILLIAM: I'm Eddie Gilliam. I'm a  
22 Certified Family Nurse Practitioner with University

1 Physicians in Tucson, Arizona.

2 DR. TONG: Good morning. I'm Ted Tong.  
3 I'm a professor of pharmacology, toxicology and  
4 pharmacy practices at the University of Arizona in  
5 Tucson, Arizona, and I'm a consultant to the  
6 Nonprescription Drug Advisory Committee.

7 DR. D'AGOSTINO: I'm Ralph D'Agostino from  
8 Boston University, biostatistician and consultant. ,

9 DR. BLEWITT: I'm George Blewitt, industry  
10 representative to the Nonprescription Drugs Advisory  
11 Committee.

12 DR. MCKINLEY-GRANT: I'm Lynn McKinley-  
13 Grant. I'm a dermatologist at the Washington Hospital  
14 Center and clinical associate professor at George  
15 Washington University and a member of the  
16 Nonprescription Drug Advisory Committee.

17 DR. KODA-KIMBLE: I'm Mary Ann Koda-  
18 Kimble, professor of clinical pharmacy at the  
19 University of California at San Francisco.

20 CHAIRMAN BRASS: I'm Eric Brass, Chair of  
21 the Department of Medicine, Harbor-UCLA Medical  
22 Center.

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1 MS. STOVER: Rhonda Stover, FDA, Acting  
2 Executive Secretary for this committee.

3 DR. RICE: Good morning. Roselyn Rice,  
4 Regional Medical Director for Quality Management,  
5 Cigna HealthCare, consultant, anti-infectives for the  
6 FDA.

7 DR. MAKI: I'm Dennis Maki, Professor of  
8 Medicine at the University of Wisconsin and a  
9 specialist in infectious disease and critical care  
10 medicine.

11 DR. LARSON: Elaine Larson, Dean,  
12 Georgetown University, School of Nursing.

13 MS. LUMPKINS: Debbie Lumpkins, regulatory  
14 review microbiologist for the Division of OTC Drug  
15 Products.

16 DR. KATZ: I'm Linda Katz, Deputy Director  
17 of the Division of Over-the-Counter Drug Products.

18 CHAIRMAN BRASS: And Dr. Katz will be  
19 making some opening remarks on behalf of the FDA.

20 DR. KATZ: I'd like to welcome everyone  
21 this morning to our NDAC meeting, and I'd like to  
22 especially thank Dr. Brass, who has agreed to be our

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1 Acting Chair or this committee, and also to thank all  
2 of those invited guests who have agreed to participate  
3 this morning.

4 The discussion this morning is really to  
5 focus on the effectiveness testing of final  
6 formulations for the over-the-counter health care  
7 antiseptic products. Today's discussion will,  
8 hopefully, be very lively, going through different  
9 kinds of performance testing measures and issues  
10 related to final formulation testing.

11 What we are hoping is that today's meeting  
12 will actually be a discussion, not just from around  
13 the table, but we also will invite those in the  
14 audience who may feel that they have information to  
15 contribute as well and may also not have been invited  
16 to be speakers to join in with some of the  
17 conversation and discussion, so that we can gain the  
18 most information that we can about how to go about  
19 final formulation testing.

20 Thank you.

21 CHAIRMAN BRASS: Thank you, and I think  
22 Debbie Lumpkins has some additional opening remarks.

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1 MS. LUMPKINS: Good morning. Today's  
2 discussion will focus on what constitutes an  
3 appropriate demonstration of a topical antimicrobial's  
4 ability to meet certain performance expectations.

5 To set the stage for today's discussion,  
6 I'd like to provide some background on the scope of  
7 the products under discussion and give you an example  
8 of a currently proposed performance expectations and  
9 testing for a topical antimicrobial product.

10 The scope of OTC antimicrobials under  
11 discussion today encompasses wash products that are  
12 used from everyone from food handlers to health care  
13 professionals in a variety of situations.

14 The topical antimicrobial drug products  
15 being discussed are currently undergoing evaluation as  
16 part of the OTC drug review. Over the course of the  
17 review, a number of performance expectations have  
18 been defined for these products.

19 In general, each drug product category is  
20 defined by its particular performance expectations.  
21 The majority of performance expectations have been  
22 associated with the antimicrobial activity of the

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1 product, and are: The speed of antimicrobial  
2 activity; the spectrum of its activity; the  
3 persistence of its effect; and the effectiveness of  
4 the product against resident versus transient  
5 microorganisms. However, not all of the performance  
6 expectations that have been proposed for these  
7 products relate to antimicrobial activity.

8 A low potential for irritation has also ,  
9 been proposed as a performance expectation.

10 As an example, a health care personnel  
11 hand wash is defined as: An antiseptic preparation  
12 designed for frequent use. It reduces the number of  
13 transient microorganisms on intact skin to an initial  
14 baseline level after adequate washing, rinsing and  
15 drying. It is broad spectrum, fast acting and, if  
16 possible, persistent.

17 In lieu of clinical testing of such  
18 products, currently proposed testing focuses on  
19 whether or not a health care personnel hand wash is  
20 able to demonstrate that it has the previously defined  
21 antimicrobial attributes through in vivo and in vitro  
22 testing.

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1                   This testing relies on microbial  
2 reductions as surrogate markers for clinical  
3 effectiveness. The demonstration of a low potential  
4 for irritation is not currently required.

5                   So continuing with the health care  
6 personnel hand wash example, it is currently proposed  
7 that a product of this type demonstrate that it is  
8 broad spectrum by measuring the minimum inhibitory ,  
9 concentration of the product against an array of  
10 laboratory strains and fresh clinical isolates of  
11 bacteria associated with nosocomial infection.

12                   The proposed definition is specific to  
13 professional use products like health care personnel  
14 hand washes, and it has been proposed that products  
15 used by consumers or food handlers have a different  
16 definition of broad spectrum to demonstrate that a  
17 product is fast acting, an in vitro time kill study  
18 delineating the kinetics of the antimicrobial  
19 activity. That is, the kill rate has been proposed.

20                   To demonstrate activity against resident  
21 versus transient bacteria, an in vivo hand wash trial  
22 conducted using the product's label directions for use

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1 is currently proposed. Activity against transient  
2 bacteria is demonstrated by the product's ability to  
3 reduce the number of marker organisms from  
4 artificially contaminated hands.

5 In order for a health care personnel hand  
6 wash to be considered effective, it must demonstrate  
7 a 2 log 10 reduction within five minutes after the  
8 first wash and a 3 log 10 reduction within five  
9 minutes after the tenth.

10 Persistence is an optional characteristic  
11 for health care personnel hand washes, and such  
12 products are not currently required to demonstrate  
13 persistence of effect. For these products for which  
14 persistence is a required performance expectation,  
15 persistence is demonstrated by the results of an in  
16 vivo test.

17 To demonstrate persistence, bacterial  
18 counts on the hands cannot exceed baseline counts for  
19 six hours.

20 Even though the example that I've given  
21 you today is specifically for health care personnel  
22 hand wash, it is illustrative of the general

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1 characteristics for, which all proposed testing for the  
2 categories under the review are.

3           These general characteristics are: That  
4 they relate to the antimicrobial expectations of the  
5 product; they involve both in vitro and in vivo  
6 testing; and they use surrogate markers for  
7 demonstration of effectiveness.

8           Today we'll hear from a variety of ,  
9 perspectives on this issue. As you listen to today's  
10 presentations, please keep in mind the following  
11 discussion points. I've paraphrased these for the  
12 sake of the slide.

13           In general terms, what is the appropriate  
14 test or tests for the previously discussed performance  
15 expectation -- that is, broad spectrum, fast acting,  
16 resident versus transient, and low irritation  
17 potential?

18           Also, should these testing requirements be  
19 based on the intended use of the product and, if so,  
20 how?

21           As Dr. Katz said, we're looking forward to  
22 a lively discussion today, and perhaps even a

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1 reevaluation of the currently proposed way of  
2 demonstrating the performance characteristics of these  
3 products.

4 If there are no questions, I'm done.

5 CHAIRMAN BRASS: Are there any questions  
6 from the panel? Thank you.

7 Our first series of discussions will focus  
8 on performance expectations and testing requirements ,  
9 for antimicrobial wash products. While we would like  
10 there to be a lively discussion, I think, unless there  
11 is an urgent point of clarification, each presenter  
12 should be allowed to finish their individual talk, and  
13 then we will look for questions after each.

14 The first speaker will be Michael J.  
15 Dolan, Vice President of Gojo Industries, who will be  
16 speaking on performance expectations, attributes and  
17 indications.

18 MR. DOLAN: Yes. Good morning. Thank  
19 you, Mr. Speaker.

20 I was going to entitle the talk "A  
21 celebration of the fourth anniversary of the 1994  
22 TFM," but we thought better of it, and changed it to

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1 performance expectations and testing requirements for  
2 antimicrobial wash products.

3 As you mentioned, I'm Mike Dolan. I'm  
4 with Gojo Industries. Just for some background, we've  
5 been in business about 50 years. We develop and sell  
6 a variety of skin care products, primarily for  
7 occupational uses, which include a number of topical  
8 antimicrobials, both of OTC type as well as new drug ,  
9 type.

10 The specific topic today is topical  
11 antimicrobial products. I thought we would give just  
12 a brief view of what we mean by these products, for  
13 those of you who are not real familiar with them.

14 These are basically products that are sold  
15 today over-the-counter or nonprescription. The ones  
16 of specific interest today are covered by monograph  
17 process. The last issued monograph was a tentative  
18 final proposed rule in 1994.

19 The topic of today is primarily the  
20 products covered by that monograph, although we will  
21 make reference in some of our presentations to some  
22 new drug products, because they illustrate certain

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1 points we want to make about the category of topical  
2 antimicrobials.

3 These include a number of product types,  
4 such as hand washes, body washes, rubs, in a variety  
5 of physical forms. These include bar soaps, for  
6 example, liquid soaps, hand gels, dips, sprays, a  
7 number of different product types; but all these are  
8 typically used in a skin antiseptis type situation.

9 The specific topics, as we understand them  
10 and will address today, are the questions before the  
11 panel. One is the performance expectations for the  
12 antimicrobial antiseptic drug products. The second  
13 one is appropriate testing for various performance  
14 characteristics that achieve these performance  
15 expectations and, finally, should the requirements be  
16 based on intended use.

17 Just a real brief history of how we got to  
18 where we are today. The original monograph  
19 proceedings go back quite a ways. In September 1974  
20 there was a panel recommendation in terms of topical  
21 antimicrobials that included seven categories of  
22 products, ranging from the antimicrobial soaps to

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1 surgical scrubs.

2 This resulted in a tentative final or  
3 proposed rule in 1978, which included those seven  
4 categories, and made recommendations about them.

5 Several of these were separated out, four  
6 through six, in the 1991 first aid monograph. So what  
7 we have now is a segregation of categories where some  
8 of these products disappeared into a separate ,  
9 monograph area and are covered there, the final  
10 monograph then being a tentative final that we're  
11 discussing today in 1994, which rolled over health  
12 care personnel hand wash, but not included the topic  
13 of antiseptic hand wash as an alternate statement of  
14 identify, as well as health care personnel hand wash,  
15 carried over surgical scrub and preoperative skin  
16 prep, but also contained a request for information on  
17 food handling antiseptic products.

18 So we will deal with these in certain ways  
19 today also. So the monograph today, as it's proposed,  
20 is significantly different than where the panel  
21 started where the initial monograph in the area came  
22 out, and we'd like to address those differences,

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1 because we think there are significant issues there.

2 We have just a few key messages that we'd  
3 like to convey today. The first is that the health  
4 care continuum model that we developed as a response  
5 to the 1994 TFM, we believe, is still a very viable,  
6 useful frame of reference to consider when using --  
7 upon applying regulations to the health care  
8 antiseptic products.

9 The model -- I will go into very little  
10 detail today, because you have all received background  
11 material on it. I notice some of the panel members  
12 who attended the symposium last year in Washington  
13 that dealt specifically with the ACCM model. I know  
14 a number of the people in the audience are familiar  
15 with it. So we will not go into much detail. We'll  
16 just summarize a couple of points about HCCM.

17 Our second message is that we believe  
18 there are clinical benefits associated with the full  
19 range of antimicrobial wash products. There are  
20 health outcomes in terms of infection risk reduction  
21 that can be attributed to all of these products across  
22 the full continuum.

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1           We will use examples of those outcome  
2 studies and data, and link them to test methodologies  
3 to show the connections and disconnections between the  
4 health outcomes that the products are to achieve in  
5 terms of performance and the testing methodologies  
6 that establish the attributes that result in that  
7 performance.

8           In answer to the second question before ,  
9 the panel, should the situational factors for the  
10 intended use direct the performance expectations  
11 assessing the requirements, our answer is absolutely  
12 yes, and we will show data why we think that is true.

13           Finally and perhaps most significantly, we  
14 have significant concerns and issues with the proposed  
15 rule as issued. In fact, if it were to issue today as  
16 written, a number of benchmark new drug products, gold  
17 standards for this type of product categories, would  
18 not meet the monograph criteria.

19           We will give specific examples of this  
20 later. We'll also go into details of methodology  
21 where we have a number of issues. We believe a lot of  
22 work is needed to finish this area.

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1           We will specifically deal in four areas  
2           with four different speakers.     I will cover  
3           performance expectations from an attribute and  
4           indication standpoint.   I'll reinforce some of the  
5           information that Debbie just presented.

6           Bruce Keswick of Proctor and Gamble will  
7           talk about some microorganism transmission data. This  
8           is new data that's not been published. We think it's ,  
9           germane to the topic.

10           We'll also talk about risk modeling and  
11           its application to other antimicrobial products and  
12           risk reduction, and finally Rhonda Jones will finish  
13           with a performance expectation conversation about  
14           linking clinical outcome data with laboratory test  
15           methodology and the implications of this to the  
16           regulatory process.

17           We go back to the health care continuum  
18           model for a minute, which was our starting point.  
19           This is based on a very simple fact that bacteria are  
20           ubiquitous.

21           Just as a side comment, let me note that  
22           the TFM specifically deals only with bacteria. It

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1 does not deal with viruses. I believe you'll see some  
2 viral data today.

3 Virus data informs us about antiseptic  
4 products and how they work, but it is specifically  
5 excluded at this point from a monograph proceedings on  
6 topical antimicrobials.

7 So we need to keep that clear in our  
8 heads. We're not talking about proposed labelling and ,  
9 indications in regards to viruses, and viral data is  
10 interesting, and it tells us something about how these  
11 products work and how we should consider them.

12 So in response to the fact that bacteria  
13 are ubiquitous, we believe that there are a number of  
14 situations where bacteria become pathogenic. This  
15 proposes a risk of infection and diseases, and that in  
16 these situations, which are defined by the specific  
17 situation, the use of antimicrobial products can  
18 reduce that risk of infection.

19 That is, plain and simple, the benefit and  
20 the thinking behind the HCCM proposal. It says you  
21 look at the category or the situation that you're  
22 involved in. That determines the type of requirements

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1       you want from an antiseptic product.

2               This then should tell you what kind of  
3       test methodology you want to use to substantiate that  
4       that product does, in fact, meet those performance  
5       expectations. That's the logic of the HCCM. That is  
6       basically the story we'll tell today.

7               Now we agree pretty much on what the main  
8       performance attributes of antimicrobial products ,  
9       should be. They should be judged on their speed of  
10      action, which typically is rapid but not necessarily.

11              For example, in a health care personnel  
12      hand wash setting you want very rapid disinfection of  
13      the hands before handling a patient. In the case of  
14      a preoperative prep, you may have a much longer  
15      tolerance for time, because the material is left on  
16      the skin as much as several hours before surgery.

17              So the situation determines what speed  
18      means, similar to spectrum of action. In general, the  
19      products are desired to be broad spectrum, but we may  
20      be talking about a situation where we're only  
21      interested in controlling the resident flora.

22              For example, on an atopic dermatitis

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1 person who has a lot of staph aureus risk, we may be  
2 primarily interested in controlling the gram  
3 positives, and that may be the spectrum we're  
4 particularly interested in for antimicrobial product  
5 for that use. Again, the situation drives the  
6 specific attribute definition.

7 Length of action or persistence: I'll go  
8 into just a bit more detail, because that one is ,  
9 somewhat more complex. Finally, some of the  
10 conversations we've had lately, such as for the food  
11 area suggest that one of the attributes may be  
12 affecting us in the presence of the soils in a given  
13 situation, particularly in the food area where some of  
14 the food handling situations have very high soil and  
15 organism loads. We may want to establish that as one  
16 of the performance criteria.

17 Expanding on persistence for a minute: We  
18 believe that persistence means that a product exhibits  
19 a prolonged or extended activity which prevents or  
20 inhibits, number one, the growth of organisms which  
21 remain on the skin after washing.

22 That is, you wash your hands. You kill a

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1 lot of the organisms. You probably don't kill them  
2 all. There are still some left. It is desirable, for  
3 example, in a surgical scrub situation for those  
4 organisms to remain very low for long periods of time.  
5 As the surgeon goes through the week, you want to keep  
6 the counts of both resident and transient quite low.

7 So persistence can mean keeping down  
8 what's already there after washing. It can also mean,  
9 though, preventing the reestablishment of transients  
10 that are contacted in the environment.

11 So there's two different perspectives on  
12 persistence here. We think there are subtle but  
13 important differences, and different products should  
14 have different persistence criteria, depending on the  
15 situation in which they're used.

16 If we take all these attributes then and  
17 apply them to the categories of products that are used  
18 as antiseptic wash products, we can see, for example,  
19 on a body wash category we may be talking either a  
20 limited or a broad spectrum, depending on whether  
21 we're talking about a patient pre-op body wash or a  
22 consumer body wash that deals primarily with resident

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1 organisms.

2           These products typically act by  
3 persistence. That is their primary effect. They're  
4 on the skin for periods of time. They act by  
5 persistence, by one of the definitions we've talked  
6 about.

7           If you go down to a health care personnel  
8 hand wash situation, these are very broad spectrum,  
9 acting on primarily transient. They need to be very  
10 fast acting. However, since they are used typically  
11 anywhere from ten to 100 times per day, the interval  
12 between washing is not high.

13           We're primarily interested in fast acting  
14 on transients. Persistence may or may not be a  
15 necessary attribute. We don't think it is a mandatory  
16 for health care personnel hand wash.

17           You can see a similar thought pattern for  
18 all of these. I won't go into detail on it, but  
19 generally we're just aligning key characteristics or  
20 attributes with situational use in category product.

21           Just a couple of quick words on  
22 indications. This is what defines the drug product.

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1 We believe this should be situationally defined. So  
2 we take the performance expectations for a given  
3 situation. That should drive the indications and  
4 labelling for a product.

5 We think that in vivo and in vitro test  
6 methodology should be the basis of substantiating that  
7 a product, in fact, meets these performance  
8 expectations for that situation.

9 Proposed labelling and indications, we  
10 believe, should be based upon validated, accepted  
11 standardized test methodologies. That really is a  
12 starting point for making indications and claims.

13 Another important point on indications:  
14 The 1994 TFM omitted indications, in fact a lot of  
15 information, on several categories of products. We  
16 believe this needs to be expanded to cover the full  
17 range of antiseptic wash products.

18 For example, nonprofessional health care  
19 settings, such as a consumer setting where there is  
20 still infection risk -- and we will show some of this  
21 information in a few minutes -- is not specifically  
22 addressed. In fact, antimicrobial soaps were admitted

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1 from the monograph.

2 Food handling -- We have begun dialogue  
3 discussions with FDA. This is an area that needs to  
4 be defined. The use scenarios are extremely complex,  
5 ranging from eating a sandwich on a picnic to a  
6 slaughterhouse. You can imagine the range of issues  
7 that we have to deal with here. So these products  
8 very much need to situational definition and  
9 indications.

10 Finally, hand sanitizers, which are  
11 basically included in the monograph, because alcohol  
12 is a category one, but we still don't have clear  
13 indications for hand sanitizer and some other issues  
14 around claims and substantiation.

15 So you can begin to see, this is a fairly  
16 complex area. It's understandable why the time frame  
17 is lagging, but we appreciate the opportunity today to  
18 present and to discuss some of the information and  
19 data we have, and we also look forward to an  
20 interesting dialogue, as Debbie mentioned.

21 Finally then, I have covered the first  
22 part of our agenda. Bruce Keswick from Proctor and

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1 Gamble will give some brief information on organism  
2 transmission that they have developed recently. Thank  
3 you.

4 CHAIRMAN BRASS: Thank you. Are these any  
5 questions for Dr. Dolan?

6 If not, as indicated, our next speaker is  
7 Dr. Bruce Keswick, who is Section Head for Clinical  
8 Research and Biometrics of Proctor and Gamble.

9 DR. KESWICK: Good morning. Can you hear  
10 me?

11 Good morning. As was said, I'm Bruce  
12 Keswick. I'm a Section Head in Clinical Research and  
13 Biometrics with the Proctor and Gamble Company.

14 Today I'm going to talk about risk in  
15 nonmedical, nonprofessional settings, cross-  
16 contamination, and transfer of bacteria, particularly  
17 in the home.

18 The points I want to make are that there  
19 are significant exposure to organisms that occur in  
20 the home; that the potential for cross-contamination  
21 is high; and that washing with plain soap is only  
22 partially effective.

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1 In the background HCCM materials there are  
2 a number of examples of both dermal and other routes  
3 of transmission where organisms can be transferred,  
4 and the risk that the general consumer has to bacteria  
5 in their everyday life.

6 I want to give a few new examples that  
7 haven't been published and a couple from the  
8 literature. Handling raw meats, eggs, sponges, dish ,  
9 towels, other items, can transmit a high level of  
10 bacteria to the hands.

11 For example, uncooked whole chicken,  
12 chicken just from a grocery store, and unwrapped and  
13 handled as if you were preparing a meal can result in  
14 up to  $10^7$  bacteria being transferred to the hands. In  
15 that case, that's per hand.

16 In the experimental situation in a study  
17 that we've conducted, if you take sterile ground beef  
18 and inoculate it with e. coli and then handle it as if  
19 you were making hamburger patties or a meatloaf, you  
20 can actually transfer up to about  $10^7$  organisms per  
21 hand.

22 Wet sponges have been shown in the

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1 literature to include even up to  $10^7$  organisms from  
2 just sitting on your kitchen sink. We took a wet  
3 sponge that was inoculated with bacteria and handled  
4 that. Ten minutes later, we found up to  $10^5$  organisms  
5 on the hands of the people who had handled those  
6 sponges.

7 If you look in the literature, there's a  
8 couple other good examples. Used kitchen towels that ,  
9 had been just in normal use for three days were  
10 handled by individuals, and then their hands were  
11 assayed. They had between  $10^2$  to  $10^3$  organisms left  
12 on their hands after touching that towel that had sat  
13 around in the kitchen.

14 Finally, another well known study where  
15 salmonella was inoculated into intact eggs and then  
16 those eggs were used to prepare -- used in  
17 preparations such as baking. Up to about 5 to 25  
18 percent of the hands that were sampled from the  
19 subjects who had handled those eggs were contaminated  
20 with that salmonella. So that there was a potential  
21 for those bacteria to be passed on.

22 In another study to show how these levels

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1 of contamination can actually be cross-transferred  
2 between food products in the home, we've done a new  
3 study. This is one where we are looking at the  
4 transfer of the organisms between chicken and using  
5 raw sterile hamburger as an indicator of the transfer.

6 Essentially, what happens in this  
7 experiment is someone handles the chicken and then  
8 handles the ground beef as if they were preparing a  
9 meal, making a meatloaf, hamburger, whatever. They do  
10 that and/or they wash their hands in between the  
11 stuff. Let's look at what happened.

12 The average cross-contamination of the  
13 ground beef after handling chicken but with no hand  
14 wash was about  $1.8 \times 10^4$  CFUs per hand. The average  
15 cross-contamination of the ground beef when hands were  
16 washed after chicken exposure still was  $3 \times 10^3$  CFUs  
17 per ml. A significant amount of bacteria remained.

18 So in summary, we feel that there's a  
19 significant risk of bacterial contamination and  
20 transfer that exists in nonmedical settings such as  
21 the home. Washing with plain soap is only partially  
22 effective, and there is a role for antibacterial

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1 products in the nonmedical/nonprofessional situation.

2 I've given some examples of the risk that  
3 might occur in the nonprofessional setting and at  
4 home, and now Dr. Chuck Haas will present how risk  
5 modeling can be used to estimate the effectiveness of  
6 antimicrobial products.

7 CHAIRMAN BRASS: Can I just ask a quick  
8 question? In our interest of testing, what was the  
9 duration of hand washing with plain soap in the  
10 experiment you just described?

11 DR. KESWICK: I can tell you. It's right  
12 here. Hands were washed for 30 seconds, rinsed for 15  
13 seconds, and then dried with a paper towel.

14 CHAIRMAN BRASS: Thank you. Are there any  
15 other questions?

16 DR. MAKI: What was the n on that  
17 experiment?

18 DR. KESWICK: I have to look. I think  
19 that was 30, but I'm not certain.

20 CHAIRMAN BRASS: Dr. Koda-Kimble?

21 DR. KODA-KIMBLE: Was the experiment done  
22 with antimicrobial hand wash?

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1 DR. KESWICK: No, that was with plain  
2 soap.

3 DR. KODA-KIMBLE: Okay. You don't have  
4 any data with --

5 DR. KESWICK: That's right.

6 CHAIRMAN BRASS: Are there any other  
7 questions from the panel?

8 Our next speaker is Dr. Charles Haas, the  
9 Betz Chair Professor of Environmental Engineering at  
10 Drexel University.

11 DR. HAAS: Thank you. Good morning,  
12 ladies and gentlemen. I'm Chuck Haas from Drexel  
13 University, and I'm appearing today as an independent  
14 consultant.

15 I've been engaged in risk assessment work  
16 for microbiological agents for about 15 years in a  
17 variety of settings, and our use of microbiological  
18 risk assessment stems directly from the 1983 National  
19 Research Council paradigm that's been widely used for  
20 chemical risk assessment, which we applied to  
21 microbials.

22 The advantage of microbial risk assessment

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1 is it permits an assessment of the consequence of an  
2 exposure in the absence of direct experiments on human  
3 subjects which might not even be doable if you're  
4 projecting for a new scenario.

5 Microbiological risk assessment has been  
6 used by a number of Federal agencies elsewhere outside  
7 the purview of this particular panel. My greatest  
8 experience is in water, both drinking water and  
9 surface water, where EPA has made use of the  
10 methodology in developing a number of regulations in  
11 those areas.

12 It's being looked at actively now in the  
13 food area by both USDA and FDA, CFSAN at FDA in  
14 particular.

15 The two applications I want to present to  
16 you today are an application of this methodology to a  
17 body wash scenario to model projected benefits of  
18 antimicrobial body wash products, and in a hand  
19 washing scenario to examine risk reduction by the use  
20 of the antibacterial hand washing contamination versus  
21 a control versus a plain soap.

22 Now in the body wash scenario, I'm

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1 focusing on staphylococcus aureus as the organism of  
2 concern. This is a dataset on dose response done by  
3 Singh in 1971, which looked at infection as a function  
4 of initial dose of staph aureus, and responses were  
5 measured up to day six in these subjects.

6 The analysis of this data is somewhat  
7 complicated by the fact that staph aureus will grow  
8 and perhaps decay dynamically upon contact with skin.  
9 Our examination of the Singh data suggests that the  
10 risk appears to be both a function of dose and the  
11 time of contact, which allows growth with the skin.

12 Therefore, to understand the dose response  
13 relationship we also simultaneously need to understand  
14 the growth kinetics of the organism in that  
15 experiment.

16 So in order to do that, looking at the  
17 Singh data, we analyzed it using a growth model. The  
18 basic details of the growth modeling are that we used  
19 a logistic growth law to model microbial growth.  
20 Concomitant with that, we have antimicrobial activity  
21 on the skin, depending upon washing with previous  
22 agents. The antimicrobial activity appears to decay

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1 exponentially with time after washing.

2 We calibrate the growth model by using the  
3 data, the Singh, which reported skin concentrations of  
4 staph aureus over day one to six, and in order to  
5 model dose response relationships what appears to work  
6 best with this dataset is the so called area under the  
7 curve approach, which is an approach that's used  
8 fairly widely in chemical risk assessment where you  
9 integrate some particular toxic concentration with  
10 respect to time.

11 So area under the curve in this context  
12 really represents time integrated microbial  
13 concentration on the skin.

14 So this is the dose response curve fitted  
15 to an exponential dose response relationship, which  
16 I've used in a number of contexts for bacteria,  
17 viruses and protozoa. The points represent the data  
18 points of Singh. The curve represents the best fit,  
19 and the fit is highly significantly statistically  
20 using a maximum likelihood fit test. Decay represents  
21 a dose response parameter.

22 So now we can use the dose response

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1 parameter from that study along with the growth  
2 relationships to estimate the impact of various use  
3 scenarios in the context of a body wash product.

4 To do this, we've also made use of another  
5 dataset that was taken by Hilltop Laboratories, also  
6 on staph aureus where die-off and regrowth on skin  
7 were followed following the use of a consumer  
8 antimicrobial bar soap in one group of subjects,  
9 versus a plain or control soap on another group of  
10 subjects.

11 Seven washings over a three-day period  
12 were performed, and then the challenge organism, staff  
13 aureus, was administered to one group of subjects,  
14 either immediately after the last wash or 24 hours  
15 after the last wash.

16 From this, we could calibrate the exposure  
17 model and use that to estimate risk of infection based  
18 on the dose response curve from Singh.

19 This represents the fit of our model to  
20 the Hilltop Lab studies. The red lines represent both  
21 the experiment -- The red points on the red lines  
22 represent the experimental observations and fit to the

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1 control.

2 So the green points and green lines  
3 represent the antimicrobial. There are two sets of  
4 lines, because one set of data and models represent  
5 the subjects who were administered the microbial  
6 challenge immediately after the last wash, and the  
7 other represents the subjects who were administered  
8 the microbial challenge 24 hours after the last wash. '  
9 So there's decay in potency.

10 A very, very good fit of the observations  
11 to the model. From this now, we could project what  
12 consequences are of particular use scenarios, and the  
13 scenario that I looked at for the purpose of the  
14 calculation was to suppose that initial staph aureus  
15 inoculum of 100,000 organisms per square centimeter  
16 occurred just after washing with either a control soap  
17 or a germicidal soap.

18 The parameters from the Hilltop Lab  
19 studies were used to assess that data, as was the dose  
20 response relationship from the Singh data, and now we  
21 examine the risk of infection over a 24 hour period  
22 from that loading, assuming no intervening washing

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1 within that 24 hour period.

2 Based on this -- and I would focus your  
3 attention here to the last column of the table -- we  
4 project out the risk to subjects under those two use  
5 scenarios, and based on this assessment of the body  
6 wash situation, there's about a twenty-fold difference  
7 in risk from control soap versus the antimicrobial,  
8 based on this data.

9 Okay. Now I would like to proceed to the  
10 second scenario, which is exposure in a hand washing  
11 situation.

12 After contact with some source of  
13 contamination, perhaps the chickens, as Dr. Keswick  
14 described, for example, or other sources of soil or  
15 contamination, there is an initial challenge of  
16 organisms. In the intervening time that would elapse  
17 between that source of contact with the challenge and  
18 a hand-to-mouth transfer within the same subject,  
19 there is a potential for either regrowth or decay of  
20 the organisms to occur.

21 Some fraction of the organisms remaining  
22 on the hand at that point then is transferred to the

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1 mouth and represents an oral ingested dose. So  
2 simply, if you multiply those three numbers together,  
3 you get an estimate of the dose of organisms that  
4 would be transferred as a result of that single  
5 instance.

6 To assess the parameters pertinent to that  
7 scenario, we've used a dose response curve of  
8 Shigella, and I should just comment here .  
9 parenthetically -- I know there's a lot of interest of  
10 late in enterohemorrhagic e. coli.

11 There is some suggest that the potency of  
12 enterohemorrhagic e. coli is similar to the potency of  
13 Shigella, although there is no human dose response  
14 data available, fortunately, to test that; but it has  
15 been used in a number of circumstances to model the  
16 potency of that organism.

17 So we used the dose response of Shigella,  
18 a loading of  $10^6$  to  $10^7$  CFU per gram, based on fecal  
19 material, transference of that material to hands as  
20 estimated by soil contact data. There's a rich  
21 literature in the field from the environmental field  
22 on how many milligrams of soil are transferred to

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1 hands as a result of various contact scenarios.

2 Reduction on the hands is estimated based  
3 on tests that were performed on reduction by Serratia  
4 Marcescens in the one-wash version of the health care  
5 personnel hand wash test, and finally ten percent  
6 transference from hands to mouth is assumed as the  
7 last stage in the process.

8 Now with that, and also running the  
9 relevant uncertainties in a Monte Carlo context here,  
10 there are two curves that are developed. The red  
11 curve represents the projected results from the use of  
12 plain soap. The green curve represents the projected  
13 results from the use of the antimicrobial soap.

14 I've highlighted here the medians of those  
15 probability distributions, and there's about a tenfold  
16 reduction in risk at the median point, as contrasted  
17 between those two agents.

18 So the take-home lesson I would offer here  
19 is that improving the immediate germ reduction via the  
20 use of a germicidal hand soap in this scenario appears  
21 to provide a significant reduction in risk.

22 Finally, let me highlight three bullets I

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1 would like to leave you with. First of all, I believe  
2 that the methodology of microbiological risk  
3 assessment is applicable to the exposure scenarios  
4 I've described here, or certainly related exposure  
5 scenarios.

6 Second, it does provide a route to benefit  
7 assessment which does not require large human trials.

8 Third, the application of MRA to the  
9 scenarios here indicates substantial benefit to  
10 antimicrobial product usage.

11 Thank you.

12 CHAIRMAN BRASS: Thank you. Are there any  
13 questions from the panel? Yes?

14 DR. GILLIAM: On your first --

15 CHAIRMAN BRASS: Please use the mike.

16 DR. GILLIAM: On the first graph where you  
17 talked about body wash, you showed that there was a  
18 20-time reduction in the risk.

19 DR. HAAS: Yes.

20 DR. GILLIAM: Was that with the group that  
21 was inoculated immediately after hand washing or 24  
22 hours later, or both?

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1 DR. HAAS: No. In that scenario, I'm  
2 simply looking at inoculation immediately after body  
3 wash.

4 CHAIRMAN BRASS: Dr. Maki.

5 DR. MAKI: It's sort of an inelegant  
6 statistical tour de force, but I'd make the  
7 observation that trying to extrapolate too much from  
8 this type of a model can be very hazardous.

9 You're working here based on your  
10 assumptions based on laboratory adapted strains, very  
11 small numbers of individuals that you have data on the  
12 kinetics of what's happening on the skin, and trying  
13 to extrapolate to a huge range of pathogenic  
14 microorganisms that may have very different behavioral  
15 patterns, very different ecologies on different  
16 individuals that influence these kinetics on which you  
17 base these descriptive equations.

18 You might find a very different real world  
19 than the modeling might suggest.

20 DR. HAAS: No, I agree, but then let me go  
21 from there to another benefit in the methodology.  
22 Having established a model like this, you can ask a

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1 "what if" question. What if the growth rate was ten  
2 times greater? What if, and so forth? See if those  
3 factors could, in fact, make a substantial difference.

4 CHAIRMAN BRASS: If there are no other  
5 questions, thank you.

6 Our next speaker will be Rhonda Jones,  
7 President, Scientific and Regulatory Consultants, Inc.

8 MS. JONES: Good morning. We are now at  
9 the final piece to the industry presentations. My  
10 name is Rhonda Jones. I'm a registered microbiologist  
11 and President of Scientific and Regulatory  
12 Consultants. I'm pleased to be here today to address  
13 you on performance expectations of topical  
14 antimicrobial wash products.

15 Briefly, I'd like to set the stage using  
16 an overview of background information on attributes  
17 and test methodology in order to directly address the  
18 first discussion point put forward by the FDA. This  
19 will be followed by a brief overview of many  
20 outstanding issues of the testing conditions and  
21 methodologies outlined in the 1994 TFM.

22 Finally, I'd like to address several

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1 formulations in order to illustrate their  
2 effectiveness, first, as the performance criteria and  
3 methodology outlined in the 1994 document, as well as  
4 reviewing specific publications on each of these  
5 formulations detailing positive clinical outcomes.

6 One of the six assumptions underlying the  
7 health care continuum model is the necessity of having  
8 standardized, defined and peer reviewed methodology to  
9 encourage reliability, reproducibility and  
10 comparability of test results.

11 So how do we get there? What's the  
12 process? We must first achieve method  
13 standardization. Although there are several  
14 organizations which develop test methodology,  
15 historically the American Society of Testing and  
16 Materials, ASTM, has been responsible for generation  
17 and adoption of methods in the area of topical  
18 antimicrobial products.

19 We recommend that this practice continue  
20 rather than the agency being responsible for detailing  
21 methodology. We believe that this offers a degree of  
22 flexibility, and yet meets the needs of standard,

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1 defined and peer reviewed methods.

2           Upon arriving at or returning to standard  
3 methods, validation of these methods will be necessary  
4 and may utilize some of the formulations I will  
5 discuss momentarily. This will then allow the  
6 selection of appropriate statistical methods and  
7 performance criteria which will be based on clinical  
8 outcomes.

9           So where are we in the process today? The  
10 TFM included modifications to methodology which are  
11 not supported by historical data nor are they part of  
12 the existing ASTM published methods. The change in  
13 test parameters are not well defined, and thus the  
14 methods may not elucidate the appropriate product  
15 attributes.

16           In addition, use situations may not be  
17 reflected by some of the proposed methodologies, and  
18 effectiveness criteria may not be linked to clinical  
19 data.

20           The following three slides are a direct  
21 response to the first discussion question put before  
22 the panel by Debbie Lumpkins this morning. The tables

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1 simply pair the test methodology available today to  
2 evaluate the microbial effectiveness of each of the  
3 six health care continuum model categories with each  
4 of the attributes as discussed.

5 I have also denoted, using an asterisk,  
6 the methodologies have been proposed in the TFM. So  
7 for measurement of spectrum, we have minimum  
8 inhibitory concentration tests, time kill testing.  
9 For speed of kill, we may utilize time kill testing,  
10 AOAC chlorine equivalency tests, and various in vivo  
11 methods.

12 The AOAC tests -- you may not be familiar  
13 with -- is being carried over from the USDA regulation  
14 of products in the food handler area.

15 For in vivo effectiveness against  
16 transient flora, there are several methods at our  
17 disposal: The health care personnel hand wash; a  
18 draft method cited here as the hand rub which is based  
19 on Rotter's publications; the cup scrub methodology  
20 agar patch, a generally used hand wash test; and skin  
21 preoperative preparation.

22 For in vivo effectiveness against resident

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1 flora, we have the modified Cade cup scrub, surgical  
2 scrub, and preoperative preparations.

3 Finally, persistent activity may be  
4 measured by the health care personnel hand wash, the  
5 general use hand wash test, modified Cade, surgical  
6 scrub, preoperative preparation, cup scrub or Rotter  
7 patch.

8 In the industry response to the monograph ,  
9 we offered a detail explanation of the various issues  
10 with each of the testing conditions and methodologies  
11 proposed by the FDA. These issues need to be resolved  
12 prior to proceeding with method validation.

13 Briefly, I would like to outline these  
14 issues for each method proposed in the monograph. The  
15 National Committee for Clinical Laboratory Standards'  
16 MIC test is proposed test the in vitro antimicrobial  
17 spectrum. However, that method was optimized for  
18 clinical laboratory testing and may not be appropriate  
19 for testing antimicrobial active ingredients or final  
20 formulations, due to insolubility or interferences due  
21 to the growth media.

22 In addition, the type, source and strain

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1 of the test organisms remains unsettled, and lastly,  
2 we have proposed a differentiation in the extent of  
3 testing necessary for active ingredients versus their  
4 final formulations.

5 Next we have the time kill test, which is  
6 a method to evaluate the rate of bacteriocidal  
7 activity. Although initially no protocol was  
8 specified, we answered the FDA's request for such a  
9 method which was submitted to the ASTM and is  
10 currently under review for adoption. However, we  
11 recognized that this type of testing may not be  
12 appropriate for all formulations, especially waterless  
13 formulations and other formulations which may have  
14 insolubility issues.

15 Also, no performance criteria was  
16 specified, and additional questions remain regarding  
17 contact times, -- those proposed by the FDA do not  
18 simulate the use setting -- growth media, test  
19 concentration, and the appropriate test controls.

20 For the health care personnel hand wash,  
21 although the ASTM methodology was cited in the  
22 proposed rulemaking and is part a duplicate of this

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1 method, several key changes were made in the 1994  
2 proposed rule.

3           These changes have not been validated, and  
4 stand in deference to a large body of historical data.  
5 These changes may affect the reproducibility of the  
6 method, and have not undergone the ASTM peer review  
7 process.

8           Other issues with the proposed rule remain  
9 uncertain, such as baseline collection, the  
10 incorporation of immediate neutralization, the hands  
11 contamination and sampling techniques, the performance  
12 and statistical criteria.

13           As it is key to a later discussion,  
14 neutralization is a technique utilized in  
15 bacteriocidal tests to halt further antimicrobial  
16 activity at a desired time point. Recent research has  
17 shown that the health care personnel hand wash and a  
18 surgical scrub test methodology has historically had  
19 inadequate neutralization, thus producing exaggerated  
20 effectiveness data. I will illustrate this shortly  
21 with some data from the literature.

22           The ASTM surgical scrub methodology is

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1 also detailed in the 1994 TFM. Similarly, the  
2 outstanding issues with this method are the need for  
3 immediate neutralization, inappropriate performance  
4 and statistical criteria, testing controls and  
5 sampling times.

6 Finally, the proposed rule cited for the  
7 ASTM standard for evaluation of skin preoperative  
8 preparations: Although the proposed rule again cited  
9 the ASTM technique, there were many areas to be  
10 delineated, including the criteria for baseline  
11 populations for the test sites, the possible need to  
12 utilize occlusion to achieve baseline for the dry  
13 site, the performance criteria, the statistical  
14 criteria, and the appropriate controls for the test.

15 So now to move in a different direction  
16 and to better demonstrate the need to revisit some of  
17 the test methods and test conditions as proposed by  
18 the 1994 monograph, and certainly the performance  
19 criteria, I'd like to introduce five examples of  
20 formulations which offer a unique analysis of the test  
21 methodology and performance expectations.

22 These models have been selected based on

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1 the availability of laboratory data such as that  
2 required by the health care continuum model or the  
3 TFM. In addition, some of the examples cited are  
4 linked with clinical studies or publications  
5 describing positive clinical outcomes.

6 Some of the examples are recognized  
7 formulations within the health care industry, such as  
8 Chlorhexidine and povidone iodine. Through the use of  
9 these examples, I would like to show that formulations  
10 with demonstrated clinical outcomes fall short of the  
11 current performance criteria proposed in the TFM.

12 Our first example features chlorhexidine  
13 gluconate or CHG containing formulations. As these  
14 formulations are not over-the-counter drugs, they  
15 require new drug applications, which involves an  
16 extensive review of safety, efficacy and chemistry  
17 data, as well as the manufacturing processes for each  
18 individual formulation prior to its introduction to  
19 the market.

20 Chlorhexidine formulations are considered  
21 to be among the most effective available for health  
22 care professionals today to prepare surgical sites, to

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1 prepare the OR team for surgery, and to reduce  
2 nosocomial infections.

3 There is an extensive database of in vitro  
4 and in vivo and clinical data to demonstrate the  
5 effectiveness of these formulations. Due to time  
6 constraints, we will focus only on the in vivo data  
7 available for each of these examples.

8 This messy table lacking the bottom line '  
9 here -- who knows where these things go with these  
10 electronic presentations -- illustrate data generated  
11 on multiple four percent CHG formulations and a two  
12 percent CHG formulations in the ASTM health care  
13 personnel hand wash test.

14 As stated earlier by Debbie, this test  
15 measures the bacteriocidal activity and removal  
16 utilizing Serratia marcescens as a marker transient  
17 organism. The table specifies specifically where  
18 delayed neutralization is used and immediate  
19 neutralizations, so that you can see the impact on the  
20 actual log reduction values as we move through the  
21 table.

22 The performance criteria for the --

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1 proposed by the TFM is listed across the top in blue,  
2 two logs of reduction at the first wash, three logs of  
3 reduction at the tenth wash, as Debbie noted.

4 In red, you see everywhere these  
5 particular formulations fail the performance criteria  
6 recommended by the TFM. Again, very obviously, a part  
7 of what is going on here is the need for immediate  
8 neutralization.

9 You can see that with delayed  
10 neutralization the log eduction values are much higher  
11 as the activity of the antimicrobial continues after  
12 sampling.

13 The data clearly show the decrease in the  
14 log reduction when immediate neutralization is  
15 employed. However, when effective and well respected  
16 chlorhexidine formulations are properly and  
17 immediately neutralized, they do not pass the  
18 performance criteria proposed in the 1994 TFM for use  
19 as a health care personnel hand wash.

20 The ASTM surgical scrub test was used to  
21 generate the data shown in this table. The surgical  
22 scrub test measures the reduction in resident flora

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1 following a standard surgical scrub procedure.

2 The reductions are measured after a single  
3 scrub on day one, the second scrub on day two, and  
4 eleven scrubs later on day five. Again, the TFM  
5 performance criteria is listed in blue. One log  
6 reduction, two, and three logs of reduction at each of  
7 the different sampling points is what is proposed.

8 Again, that particular methodology employs  
9 delayed neutralization. As you can see from the data  
10 shown here, delayed neutralization again allows for  
11 much higher log reductions; whereas, when the  
12 formulations are immediately neutralized, you begin to  
13 see the impact of instantaneously stopping that action  
14 as you're recovering the bacteria off of the hand.

15 In red we see where each formulation has,  
16 in fact, failed to meet the performance criteria  
17 established by the TFM. Interesting to note, these  
18 are all the formulation tested by four different  
19 people.

20 Nonetheless, when chlorhexidine  
21 formulations are properly and immediately neutralized,  
22 they do not pass the performance criteria proposed in

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1 the 1994 TFM for surgical scrub use.

2 So as a review of an example provided by  
3 chlorhexidine formulations performance in these two  
4 tests, we see the need for method standardization to  
5 reduce the variability in the tests and afford greater  
6 comparability among test formulations.

7 When effectively neutralized, approved NDA  
8 formulations do not meet the performance criteria  
9 established for the TFM for OTC drug use. Thus, these  
10 effective formulations would not be available as  
11 surgical scrubs or health care personnel hand washes  
12 under the proposed rule.

13 Moving along to our next example is a 7.5  
14 percent povidone iodine scrub, which is equally well  
15 respected for its clinical effectiveness. From a  
16 regulatory standpoint, it is classified as an over-  
17 the-counter drug and as category 1 for safety and  
18 effectiveness.

19 Category 1 ingredients are considered safe  
20 and effective for each of the intended uses in the  
21 monograph. The literature includes extensive  
22 laboratory in vitro and in vivo data, as well as

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1 clinical publications.

2 This table depicts the formulation's  
3 performance in studies following the ASTM surgical  
4 scrub test. Again, the criteria are listed in blue  
5 across the top, and we have the issue of delayed  
6 neutralization in the existing test methodology. The  
7 performance criteria is one, two and three logs of  
8 reduction at each of the different time frames.

9 The first two examples show the effect of  
10 delayed -- can be compared to the immediately  
11 neutralized formulation -- to show the effect of the  
12 institution of the immediate neutralization step.  
13 Again, everywhere in red is where the formulation  
14 would be shown to fail the performance criteria.

15 Irregardless of the povidone iodine  
16 formulation neutralization, each of these formulations  
17 would fail the proposed reduction levels for surgical  
18 scrubs.

19 As the data presented here is generated in  
20 multiple laboratories on the same formulation, it  
21 further illustrates the need to strive collectively  
22 toward greater standardization of test methodology and

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1 to facilitate reproducibility and comparability of  
2 test results.

3 The povidone iodine example illustrates  
4 the variation, due to lack of standardization of the  
5 test methodology. However, whether neutralized or  
6 not, formulations with a category 1 ingredient such as  
7 povidone iodine do not meet the proposed criteria for  
8 OTC health care antiseptic drug products.

9 Our next example focuses on a one percent  
10 Triclosan formulation. Triclosan is category 3 for  
11 safety and effectiveness for health care personnel  
12 hand washes. The specific formulation we will track  
13 is newly launched in the U.S. and is substantially  
14 similar to formulations available internationally.

15 Extensive in vitro and in vivo microbial  
16 data and irritation studies have been compiled, as  
17 well as published studies suggesting a positive  
18 clinical outcome. As we want to stay on schedule  
19 today, there's just a brief time to whip down through  
20 each of these reprints, but some of the authors are  
21 going to be with us later to describe their studies.

22 The first study, published by Marshall,

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1 describes the reduction of MRSA in a hospital upon the  
2 institution of the one percent Triclosan soap for  
3 patient bathing prior to admission and hospital -- and  
4 throughout hospitalization.

5 The author reports a concomitant reduction  
6 in the presence of ciprofloxin resistant strains over  
7 the one-year period. Paul Marshall, the author of the  
8 study from Sutherland Hospital in Australia, will  
9 provide additional detail on his study later today.

10 The Webster 1991 and 1992 reports showed  
11 the effect of institution of the one percent Triclosan  
12 formulation for staff hand washing with no other  
13 infection control practice changes for a seven-week  
14 study. The formulation replaced a four percent  
15 chlorhexidine gluconate product.

16 Webster reports that new MRSA cases in the  
17 neonatal intensive care unit were reduced from 3.4  
18 percent to less than two-tenths of a percent. In  
19 addition, the staff reported less skin irritation and  
20 a higher rate of product acceptance, especially from  
21 those staff with sensitive skin.

22 Based on this prospective study, Webster

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1 and co-workers, the third citation here, began a one-  
2 year trial, continuing the same infection control  
3 regimen. The authors report a gradual elimination of  
4 MRSA from the neonatal unit, as well as the special  
5 care nursery.

6 The authors note that, although the  
7 occurrence itself is insufficient to confirm a causal  
8 relationship, it is related temporally and was  
9 duplicated.

10 The final citation by Brady and co-workers  
11 reported that, following the institution of the one  
12 percent Triclosan product for whole body bathing, in  
13 addition to routine post-operative surveillance and  
14 the reduction in antibiotic use post-operatively,  
15 coincided with the significant reduction in the number  
16 of MRSA carriers and infections.

17 So again we move to test data generated  
18 using the ASTM health care personnel hand wash test.  
19 This study was performed at 15 and 30 seconds using 5  
20 mls of product, and included a comparative two percent  
21 chlorhexidine formulation.

22 The TFM criteria is noted in blue. Two

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1 logs of reduction is required after a single wash.  
2 Three logs of reduction are required after ten  
3 consecutive washes.

4 Again listed in red are each of the time  
5 points where these formulations do not meet the  
6 performance criteria proposed.

7 It is important to note that not only does  
8 the one percent Triclosan formulation not meet the  
9 criteria, neither does the two percent chlorhexidine  
10 formulation, although the one percent chlorhexidine  
11 formulation does move slightly above the performance  
12 level for wash one, whereas the two percent  
13 chlorhexidine remains just below.

14 The one percent Triclosan example  
15 demonstrates the comparable in vivo effectiveness of  
16 a Triclosan formulation to a chlorhexidine NDA  
17 formulation when CHG is properly neutralized. The  
18 reviewed studies suggest positive clinical outcomes  
19 coincident with the institution of the one percent  
20 formulation and allow correlation to laboratory data.

21 Lastly, neither the NDA nor the one  
22 percent Triclosan formulation in this case pass the

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1 TFM requirement to be offered as health care personnel  
2 hand washes.

3 An additional Triclosan example is  
4 provided by a .3 percent formulation which is  
5 currently available for use as the health care  
6 personnel hand wash. This formulation is comparable  
7 to formulations which may be offered for consumer use.

8 Triclosan is classified as category 3 for  
9 effectiveness and safety as a health care personnel  
10 hand wash. Tracking this formulation also allows  
11 review of laboratory in vitro and in vivo data and a  
12 single report of clinical outcome.

13 In addition, the formulation has been  
14 shown to demonstrate a 92 percent and a 98 percent  
15 reduction, respectively, against hepatitis A and polio  
16 virus, as compared with lesser reductions for four  
17 percent chlorhexidine formulations.

18 This data was generated using a new ASTM  
19 test method which measures removal of viral  
20 contaminants from the fingertips of human volunteers.  
21 Dr. Syed Sattar of the University of Ottawa will  
22 address this type of testing in detail later in the

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1 program.

2 Zafar and co-workers' published clinical  
3 study reported a single change to the .3 percent  
4 formulation for hand and body washing halted an  
5 outbreak of MRSA in a neonatal unit. The authors  
6 report that the unit was free of MRSA for over three  
7 and a half years.

8 Dr. Abdul Zafar from Arlington Hospital  
9 will review their findings and their continuing  
10 success for a total of eight years later today.

11 The .3 percent Triclosan example, as  
12 evaluated again in the health care personnel hand  
13 wash, shows where the TFM, in blue again, has required  
14 two logs of reduction in the first wash and three logs  
15 of reduction in the tenth wash, again shows that this  
16 particular formulation, using a 60-second wash time  
17 with 5 mls of product, does not meet the TFM.

18 The .3 percent Triclosan formulation  
19 offers a report suggesting a positive clinical outcome  
20 concomitant with the institution of the soap. An  
21 additional study demonstrates the utility of a  
22 Triclosan formulation for viral removal. However, the

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1 formulation does not meet the TFM performance criteria  
2 to be available as a health care personnel hand wash.

3 Our final performance example today is a  
4 1.5 percent triclocarban bar soap. Triclocarban or  
5 TCC is classified as a category 3 ingredient for  
6 effectiveness, and category 1 for safety, although the  
7 particular formulation I will discuss is an NDA  
8 product.

9 For this example, we have available in  
10 vitro and in vivo laboratory studies, as well as two  
11 recent studies demonstrating a statistically  
12 significant reduction in staph aureus associated with  
13 atopic dermatitis.

14 Although Dr. Jim Leyden from the  
15 University of Pennsylvania School of Medicine will be  
16 up next to discuss this study in detail, the slide  
17 contains a brief overview of the data collected during  
18 two studies of patients exhibiting atopic dermatitis.

19 As patients with atopic dermatitis have a  
20 high frequency of colonization of staph aureus, they  
21 provide an excellent opportunity to study the  
22 effectiveness of topical antimicrobial wash products

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1 used daily for whole body bathing.

2 Both studies demonstrated a statistically  
3 significant reduction of staph aureus -- reduction  
4 values are listed here and here for the 1.5 percent  
5 TCC versus plain soap -- and an improvement in the  
6 dermatology scores, listed here -- I apologize. We've  
7 lost the lines which made it a little easier to track.

8 So both studies demonstrate a significant  
9 reduction in staph aureus and an improvement in the  
10 dermatology scores for use -- one use of the bar soap  
11 over a non-antimicrobial soap. These studies suggest  
12 a clinical improvement in dermatitis resulting from  
13 the use of an antimicrobial bar soap.

14 Again, we move to the laboratory data.  
15 This table depicts three different in vivo  
16 methodologies that we haven't really gotten into up to  
17 this point. These methodologies are used to assess  
18 antimicrobial effectiveness of the particular one  
19 percent TCC formulation.

20 The studies utilized plain soap or  
21 placebos as controls -- Again, we're missing a line  
22 here. These studies utilized plain soap or placebos

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1 suggested clinical improvement against staph aureus in  
2 atopic dermatitis cases to a range of tests proposed  
3 in the health care continuum model. In addition, the  
4 data clearly show a statistically significant benefit  
5 of the formulation over plain soap and water against  
6 transient and resident flora for immediate and  
7 persistent antimicrobial activity.

8 So to conclude, I have reviewed five  
9 performance examples in order to illustrate the areas  
10 where continued collaboration to standardize and  
11 define methodology and in order to achieve reliable,  
12 reproducible, and comparable test results.

13 The ASTM Antimicrobial Committee can  
14 provide a peer reviewed consensus process to achieve  
15 method standardization. In order to work toward this  
16 goal, the SDA/CTFA Coalition has written and submitted  
17 to the ASTM many methods where standards did not  
18 previously exist.

19 These methods have been and are continuing  
20 to be extensively peer reviewed by microbiologists  
21 expert in the field. The ASTM provides a forum by  
22 which these methods can be maintained and published.

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1           We recommend that the FDA continue their  
2 practice of citing this methodology rather than  
3 detailing the methodology in future rulemaking.

4           Finally, once achieved -- once standard  
5 methodology is achieved, it can be used to validate  
6 the methods. This will allow the meaningful selection  
7 of appropriate statistical and performance criteria by  
8 which to measure each attribute, while linking the  
9 laboratory effectiveness to positive clinical outcome  
10 reports.

11           So to take a deep breath and step back and  
12 offer a few concluding remarks overall to the industry  
13 presentations: The health care continuum model  
14 provides a useful frame of reference for evaluating  
15 these products.

16           Health benefits are associated with a full  
17 range of antimicrobial wash products. Situational  
18 factors, i.e., intended use, should direct performance  
19 expectations and testing requirements.

20           We have significant concerns with the test  
21 methodology and the performance criteria presented in  
22 the 1994 TFM. Additional work is needed before the

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1 rule is finalized. Standardized test methodology is  
2 the logical next step.

3 Thank you.

4 CHAIRMAN BRASS: Thank you. Questions  
5 from the panel? Dr. D'Agostino.

6 DR. D'AGOSTINO: I'm not sure I'm getting  
7 the message completely. Are you saying that the TFM  
8 criteria are too stringent or that there's so much  
9 variability in the method that the labs can't meet it  
10 individually, but some sort of average might make it?  
11 I'm missing --

12 MS. JONES: Well, I believe, actually, it  
13 is a combination of both, and perhaps future  
14 performance criteria would be XYZ reduction plus or  
15 minus the standard deviation of the methodology, which  
16 would come out of any validation work that was done.

17 DR. D'AGOSTINO: In some of the  
18 presentation or pieces of the presentation you made  
19 here where you just an individual lab, was that just  
20 one testing within that lab as opposed to some sort of  
21 averaging of numbers?

22 MS. JONES: Yes. The publications --

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1 typically, yes. That was one study. It may have  
2 included anywhere from six to 30 human subjects, and  
3 that may have been duplicated if there were other  
4 formulations. Typically, in the publications I  
5 selected the particular formulation, but there may  
6 have been three or four other comparative formulations  
7 also being run.

8 DR. D'AGOSTINO: It's very hard for me to  
9 sort of pull a message away when there's just an  
10 average pulled out there, and I don't have a sense of  
11 variability; but I think, just to say again, you think  
12 the criteria is too stringent, even if the variability  
13 were being taken care of?

14 MS. JONES: I believe so. I think the  
15 povidone iodine example probably illustrates that  
16 better than anything, because in all cases it was well  
17 below the performance criteria.

18 CHAIRMAN BRASS: Dr. Tong?

19 DR. TONG: In the last example of the TCC  
20 1.5 percent, was the TFM standards or tests applied in  
21 that situation, because you indicated that clinical  
22 benefit in the health care continuum model standards

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1 showed benefit, but you didn't mention anything about  
2 the other.

3 MS. JONES: I showed a health care  
4 personnel hand wash on a single wash that showed a  
5 reduction, I believe, of 2.8 logs. So that would be  
6 above the 2.0 TFM requirement. In the case of the  
7 Cade test, as well as the cup scrub test shown in that  
8 table, those were not proposed in the TFM. They have  
9 been proposed by the industry in their health care  
10 continuum model to support both the general  
11 antimicrobial hand wash and body wash categories.

12 DR. TONG: I have one other question.  
13 Could you -- Thank you. Could you comment on an  
14 earlier statement, that you indicated the industry  
15 wanted only the active ingredients to be addressed  
16 when it comes to spectrum of organisms affected and  
17 not the final formulation. Can you --

18 MS. JONES: No, no. Yes, I would  
19 definitely like to clarify that point.

20 What we suggested was actually just an  
21 alteration in volume of testing between the two. The  
22 TFM currently recommends testing on 1300 strains for

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1 both active ingredients, the formulation, the final  
2 formulation and the vehicle.

3 We believe that was somewhat onerous and  
4 that the active ingredient could be tested on a large  
5 number of strains. We suggested the strains listed --  
6 a slight modification of the strains listed in the TFM  
7 plus four clinical isolates of each, rather than 25.

8 That would be for the active ingredient, ,  
9 and then a subset of those strains was proposed for  
10 testing of final formulation, and that subset of  
11 strains was matched to the use setting. So in the  
12 case of food handlers, it would be test strains that  
13 were specific to organisms that would be of concern in  
14 food preparation or processing. It's matched to use  
15 setting.

16 DR. TONG: Thank you.

17 CHAIRMAN BRASS: Dr. Koda-Kimble.

18 DR. KODA-KIMBLE: One of the issues for  
19 the over-the-counter panel is safety, and you briefly  
20 mentioned that one product was less -- it had less  
21 irritant qualities. I have two questions.

22 One is: Does the industry have any

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1 suggestions as it relates to tests for irritation?  
2 The other issue that was brought up by the 1974 panel,  
3 was it, was a concern for overgrowth of gram negative  
4 organisms in skin wash or body wash products. Are  
5 there any concerns about that from the industry, and  
6 are there any tests you might suggest to evaluate  
7 that?

8 MS. JONES: Okay. I love multi-part  
9 questions.

10 Going back to your first original  
11 question, the group that's been assembled are  
12 microbiologists. So they are expert in this area of  
13 antimicrobials. Oh, somebody else wants to take it.  
14 Okay, great.

15 CHAIRMAN BRASS: Please identify yourself  
16 when you go to the mike.

17 DR. DOLAN: This is Mike Dolan, Gojo.

18 You'll notice on the attribute list, we  
19 did not include irritation as a primary attribute.  
20 The reason for this is we believe, based on extensive  
21 experience, that the marketplace will sort out the  
22 issue of skin irritation.

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1                   For example, I think there are a couple of  
2 dermatologists in some test labs in the room that  
3 spend a substantial part of their time demonstrating  
4 the irritation potential of these products. We have  
5 cases in our company, for example, where product  
6 switches have been very pronounced, because we've  
7 developed low irritation versions.

8                   I think everybody in the industry today is  
9 working on the balance between antimicrobial kill  
10 efficacy and skin irritation. We don't think skin  
11 irritation ought to be specified in a monograph. The  
12 marketplace itself and the development of the products  
13 will take care of that.

14                  There's routine screening of these  
15 products by skin patching testing, sensitization  
16 testing, use panels, wash tests. If there are primary  
17 irritation problems, they show up in the development  
18 and use of the products, and they disappear fairly  
19 rapidly.

20                  So we don't think that irritation needs to  
21 be a primary specified attribute.

22                  CHAIRMAN BRASS: Ms. Jones, if you could

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1 return to a microphone to answer this. Thank you.

2 MS. JONES: I believe, in the 1994 TFM,  
3 they felt that that particular issue had been answered  
4 by subsequent studies. Debbie is nodding her head.

5 CHAIRMAN BRASS: If I could ask a couple  
6 of questions.

7 MS. JONES: Sure.

8 CHAIRMAN BRASS: My first question is: '  
9 There seem to be the greatest discordance between the  
10 TFM standards and the data you presented on the day  
11 five multiple wash, higher level kill requirement. is  
12 that observation accurate, and what do you feel is the  
13 relevance, particularly for a product like a surgical  
14 scrub, of a day five/eleven scrub standard?

15 MS. JONES: The surgical scrub test, I  
16 think, was developed quite a while ago to try and  
17 mimic, at least in the eighties, what they call a  
18 standard frequency for that type of formulation.  
19 Certainly, we would expect that the fifth one might  
20 offer higher variation, and those things would be  
21 sorted out of the validation methods -- validation of  
22 the methods. So --

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1 CHAIRMAN BRASS: I'm sorry. Do you think  
2 it is appropriate to maintain as a standard a higher  
3 log kill on a day five for a product that already is  
4 effective on day one?

5 MS. JONES: I see your question. I think  
6 -- Do you want to take it, please, Dr. Leyden?

7 DR. LEYDEN: Yes, it's a good question, I  
8 think. Jim Leyden, University of Pennsylvania.

9 That original test when it was first  
10 developed in the ancient days when some of us  
11 struggled with this was proposed by people from the  
12 Sterling Research Institute, and one of the attributes  
13 that was suggested that could be useful was  
14 persistence, and it mostly revolved around  
15 hexachlorophene; and with chronic use with that  
16 particular molecule in a detergent based system you  
17 could show that over time that the effect was greater.

18 Well, it just so happened, that was the  
19 time points they picked. It wasn't that they picked  
20 those time points thinking, well, that would be a good  
21 time point to measure something if someone is going to  
22 open my heart or your brain, where you're really

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1 interested in how much can you reduce bacteria on that  
2 hand and how long will that last in terms of an  
3 operation, because presumably, if you're going to  
4 operate on you and then me, you're going to do  
5 something in between, hopefully. Yes, right,  
6 especially if I'm second, you see.

7 CHAIRMAN BRASS: Thank you. I just would  
8 like to reinforce the point Dr. D'Agostino made. In  
9 terms of evaluating the data you presented, the  
10 absence of presentation of variance and the numbers  
11 involved in each of those studies makes it very  
12 difficult to assess whether the discordance from the  
13 proposed standard is due to the inadequacy of the  
14 standard or the inadequacy of the test attempting to  
15 meet the standard.

16 In our trying to resolve that, I think  
17 those kinds of details are very, very important.

18 MS. JONES: Right. Certainly, we will  
19 provide you with the full publications that support  
20 those methodologies, so that you can look at those.

21 CHAIRMAN BRASS: Or even if you just --

22 MS. JONES: I mean, I think they've

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1 already been submitted, but not in that frame.

2 CHAIRMAN BRASS: In the summary -- Again,  
3 in trying to summarize the data, those test  
4 characteristics -- I mean those study characteristics  
5 would be very important in tabulating that kind of  
6 summary table.

7 MS. JONES: We think it's important to  
8 start by standardizing the method and then performing  
9 the validation study where you can incorporate that  
10 into the performance criteria, again XYZ log reduction  
11 plus or minus whatever the standard deviation for each  
12 of the different tests is.

13 CHAIRMAN BRASS: Thank you very much.

14 MS. JONES: Thank you.

15 CHAIRMAN BRASS: Our next speaker will be  
16 Dr. Jim Leyden from the Department of Dermatology,  
17 University of Pennsylvania, speaking on antimicrobial  
18 use in the nonmedical setting.

19 DR. LEYDEN: Thank you. Elaine Larson  
20 pointed out to me that the CV that you all have looks  
21 like I died ten years ago. So I would just tell you  
22 that, as a dermatologist, my area of -- one of my

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1 primary areas of research interest has been trying to  
2 understand what constitutes the reasons why certain  
3 groups of bacteria are found on different areas of the  
4 skin, how infections occur, the role of microorganisms  
5 in skin disease, and I spend a substantial amount of  
6 time trying to develop ways of measuring in vivo  
7 antimicrobial activities of antibiotics and non-  
8 antibiotics.

9           So I was asked if I would first present an  
10 overview of why these kinds of things may have utility  
11 in the nonmedical setting. I think there's a  
12 substantial group of individuals out there that I'll  
13 very briefly detail for you that can benefit from such  
14 products, and then say a few things about some of the  
15 methodologies other than what have been presented  
16 here, which could be considered in trying to develop  
17 ways of understanding how effective these products  
18 are.

19           I think there are enormous amounts of data  
20 available on different methodologies, all of which can  
21 provide very, very meaningful insights when well  
22 designed studies that ask specific questions are used,

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1 attention to detail like neutralization which is a  
2 major problem if it's not paid attention to, but can  
3 then be correlated, as you just heard, with clinical  
4 experiences and come up with reasonable guidelines to  
5 understand which formulas work, which ones don't,  
6 which ones work better than others.

7           Anyway, these materials are often called  
8 body washes. I think it's important to recognize -- ,  
9 or soaps. They really aren't soaps. Most of them are  
10 detergent systems. There are increasing uses of other  
11 delivery systems, lotions, foams and other things that  
12 have less irritation potential, particularly for those  
13 individuals who need to wash on a frequent basis.

14           Here are some of the more obvious, at  
15 least to me, areas where populations exist. I'll  
16 start here with the hands.

17           You've heard a little bit earlier from  
18 Bruce Keswick and, I think, the agency has recognized  
19 that there are plenty of examples of individuals  
20 having their hands contaminated by potential  
21 pathogens. I'll just very briefly show you that the  
22 integrity of the outer layer of the skin, the stratum

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1 corneum, is very important as a defense mechanism.

2           There are large numbers of individuals in  
3 this room, including myself, who have compromised  
4 stratum corneum. That makes us more vulnerable to  
5 colonization and subsequent invasion by potential  
6 pathogens, and there's a large group of individuals  
7 who carry very high numbers of staph aureus on their  
8 skin with varying degrees of immune competency and,  
9 depending on the virulence of the strain, it can be  
10 harmful potentially to that individual or to others in  
11 their environment.

12           This is the hand -- Elaine, this is Kermit  
13 -- you remember Kermit, the animal caretaker in our  
14 department -- after carefully washing his hands on his  
15 way out the door on the way home. You can see,  
16 there's an interesting mixture of gram negative, gram  
17 positive and others on his hand.

18           A patient in our clinic with chronic  
19 eczema with normal appearing hands who's got staph  
20 aureus and a variety of other organisms, and my son,  
21 the lawyer, after changing the diaper of his perfect  
22 son known now in Philadelphia as "the Dauphin," since

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1 he is attended by a variety of individuals on a 24  
2 hour basis.

3 Just parenthetically, his wife, my  
4 daughter-in-law, two weeks ago had a conjunctivitis  
5 which I cultured and grew out e. coli and staph  
6 aureus. I think the e. coli probably got there via  
7 this mechanism.

8 So that's one group I've very sketchily ,  
9 talked that others have talked about. Let me just  
10 show you the stratum corneum. In dry skin there are  
11 microscopic fissures which, when present, lead to  
12 uplifted scales that we can then see, and we call dry.  
13 This provides a portal of entry for microorganisms.

14 Many years ago we showed that Group A  
15 streptococci inoculated on totally normal skin would  
16 rapidly die, mostly because of inhibition by skin  
17 lipids, but with microscopic subclinical  
18 scarifications the same organisms would very quickly  
19 invade and begin the process of infection.

20 We've shown, years ago when we were  
21 studying various agents in terms of their effect on  
22 wound healing, in a large number of individuals that

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1 we did a variety of things with a variety of dressings  
2 that after a day or two, somewhere in the neighborhood  
3 of 30 to 40 percent of these wounds -- and this was in  
4 students at Drexel and University of Pennsylvania  
5 desperate for cash who participated in these  
6 experiments -- that about 30 to 40 percent of them  
7 became heavily colonized by strains of staph aureus  
8 which, in some cases, were virulent enough to cause a  
9 purulent -- a host reaction, but in other  
10 circumstances were at least able to inhibit and delay  
11 the process of wound healing.

12 So that's a very common potential area  
13 where people using effective antimicrobial agents on  
14 a daily basis could have residual activity, material  
15 with activity that could minimize that first all-  
16 important step of colonization before infection can  
17 take place.

18 I'd like to spend a little time on atopic  
19 dermatitis, which here you can see is obviously  
20 secondarily infected, and there are primary lesions  
21 elsewhere peripheral to the lesion.

22 Many years ago I showed that, even in

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1 clinically noninfected situations such as this typical  
2 inflamed area of atopic dermatitis, this agent non-  
3 colored slide shows you that there are hundreds of  
4 thousands to millions of staph aureus lesions in the  
5 lesions, and in skin about five centimeters away there  
6 were hundreds to thousands to tens of thousands of  
7 staph aureus, and many others have reproduced these  
8 findings.

9 Even in clinically noninfected eczema, if  
10 one uses something that reduces staph aureus counts,  
11 there is at least an improvement clinically, and I  
12 think that's a fairly well established principle in  
13 dermatology.

14 More recently, we have looked at another  
15 group of individuals with less exuberant forms of  
16 atopic dermatitis, and this paper in press in the  
17 Journal of Pediatric Dermatology, looking at these  
18 very minor dry, scaly forms of eczema. About 40  
19 percent of those lesions are colonized, whereas  
20 individuals in the dermatology clinic with non-eczema  
21 conditions, warts, etcetera -- there is also a  
22 significant colonization of lesions, about 20 percent,

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1 uninvolved skin again heavily colonized, and about 30  
2 percent of these individuals have significant  
3 colonization of their hands as well as a reservoir  
4 site such as the anterior nares.

5 Here, I'll give you an idea of the density  
6 of these,  $10^4$ , in these really non-inflamed forms of  
7 eczema, less than what one sees in the more exuberant  
8 but, nonetheless, a significant number of organisms  
9 which have varying degrees of virulent capacity. Many  
10 of these strains appear to be, fortunately,  
11 nonvirulent or at least the virulence cannot be easily  
12 demonstrated, but other individuals get colonized by,  
13 clearly, more virulent strains.

14 There's an interesting relationship  
15 between the lesion and the hand being positive. If  
16 the lesion is positive, almost for sure the hand will  
17 be positive, as will the anterior nares.

18 There's a rather substantial literature in  
19 HIV+ individuals indicating that there is significant  
20 colonization of the skin of these individuals, even  
21 when the skin doesn't look infected, and those of us  
22 who see patients know that dry, scaly eruptions over

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1 most of the body are not uncommon in these  
2 individuals, and this is teeming with staph aureus.

3 If you have the right strain present, you  
4 can get some fairly nasty at least localized  
5 infections.

6 We have a paper in press, interestingly,  
7 in -- This came out of the Desert Storm operation  
8 where staph aureus infections were a problem, as they ,  
9 have been in all -- and streptococcal infections, as  
10 they've been in all military operations over the  
11 years.

12 We looked at recruits at Ft. Dix in New  
13 Jersey. After they had been there a while, living in  
14 close quarters and doing things soldiers do, I guess,  
15 staph aureus colonization clearly is different in  
16 these individuals than it is in the rest of us. This  
17 is another area, another group, who would, I think,  
18 clearly benefit from using something that was  
19 effective.

20 Now you've heard some of the papers in the  
21 literature. There's an ancient literature back, you  
22 know, in the late sixties and seventies, that either

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1 showed or didn't show efficacy of detergent based  
2 antimicrobial substances, depending on the population,  
3 the rate of infection in the population, the number of  
4 subjects, all the usual things; but there were some  
5 that clearly showed that.

6 You heard some of the more recent studies  
7 with methicillin resistant staph aureus being  
8 eradicated by some of these detergent based materials,  
9 and you heard briefly about this study in atopic  
10 dermatitis, which was, I think, a very laborious,  
11 difficult study to do in 50 individuals who were  
12 treated either with 1.5 percent TCC or the soap  
13 without -- the detergent system without the  
14 antimicrobial.

15 These individuals also used a very low  
16 strength topical steroid once a day and, as you heard,  
17 clinical and microbiologic evaluations were done at  
18 different time points. In those treated with the soap  
19 with the antimicrobial, there was a difference in  
20 terms of clinical improvement in both the primary,  
21 secondary signs of dermatitis as well as the global  
22 overall improvement similar to the kinds of things

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1       that we and others had shown in the past with  
2       antibiotics, either topically or systemically, and  
3       that this improvement correlated with a significant  
4       difference in terms of reduction of staph aureus,  
5       which is aggravating the dermatitis.

6               So I don't think there's any question, at  
7       least in my mind, that there are lots and lots of  
8       people out there in nonmedical environments who have ,  
9       their hands contaminated and have their skins  
10      contaminated by organisms that can be harmful to  
11      themselves and/or to others in their environment.

12             So how do you test all these things  
13      without going out and doing huge field trials? Well,  
14      I think one of the things you can do is try to  
15      identify those populations who are most obviously in  
16      need.

17             You heard of now two brief overviews of at  
18      least one study in one population teeming with staph  
19      aureus. There are others, as I've very briefly shown  
20      you. Then there are a variety of antimicrobial tests.

21             I would echo what was just said before me  
22      about the proposed criteria. When it was first showed

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1 to me, I read it, and my comment was there's nothing  
2 that's currently used that will pass this test --  
3 nothing -- which means either we're all fooled, which  
4 I don't think, or that tests need to be rethought.

5 Here's an atopic dermatitis patient.  
6 There are people out there with atopic dermatitis who  
7 have persistent staph aureus on most of their hand,  
8 and it isn't rapidly dying off.

9 One of the difficulties with inoculating  
10 the e. coli or Serratia is those organisms, for most  
11 individuals, when they're dumped on the hand, they  
12 start dying right away, and you have to keep  
13 reapplying it, and you have to move quickly to do  
14 these studies in order to be able to show an effect of  
15 an agent or an antimicrobial agent; but there are  
16 individuals whose hands -- bartenders, for example.  
17 They carry a lot more gram negatives.

18 Elaine, you showed years ago nurses carry  
19 a lot more gram negatives on their hands, even though  
20 they're washing, you know, 20-30 times a day. We also  
21 showed that, depending on what unit you're in -- If  
22 you're in the oncology unit, you've got a lot more

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1 gram negatives and enteric organisms.

2 You're taking care of dermatology patients  
3 who used to be allowed in hospitals -- they're no  
4 longer allowed; they are now told to die at home  
5 quietly -- that those nurses had staph aureus on their  
6 hands.

7 So what you have on your hands can reflect  
8 who you're taking care of, and some modifications of  
9 the proposed tests seem in order to me also.

10 There are other ways of doing it, too.  
11 This is a real old slide of just wrapping up the  
12 forearm with Saran wrap. You get rapid increase of  
13 what's already there, up to millions to tens of  
14 millions. As long as you keep that hydration present,  
15 those organisms will stay there, and you have two  
16 arms, and you can do all kinds of experiments in terms  
17 of effective material.

18 Whether you use Saran wrap or something  
19 like a Hilltop chamber, you can expand this low  
20 density flora to hundreds of thousands to millions.  
21 You can also take axillary and perineal flora, which  
22 are much more varied and interesting and contain all

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1 kinds of different organisms.

2 You can take those organisms, put them on  
3 the forearm, and wrap it up with Saran wrap or a  
4 Hilltop chamber, and recreate the armpit or the groin  
5 or the toe web space on the forearm, and then you have  
6 -- you know, you have three eczella, six toe-web  
7 spaces or whatever you want.

8 Then you can do maneuvers. You could  
9 pretreat the skin for a period of time and then see  
10 how these transfer. Inocula expand or do not expand  
11 under occlusive dressings, or you can expand it and  
12 then ask can the material reduce it, and how quickly  
13 can it reduce, and does it persist over time.

14 So it gives you the ability to do, within  
15 the same subject, controls, untreated, vehicle  
16 treated, etcetera. It gives you a flexibility of  
17 doing within an individual a lot of work that makes it  
18 statistically much easier to show whether an effect  
19 did or did not take place.

20 You can use these chambers here  
21 demonstrating how much moisture accumulates under  
22 them. You can inoculate organisms. You heard briefly

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1 about staph aureus and other organisms. Gram  
2 negatives can be inoculated. They will survive.

3 Again, you can pretreat for a period of  
4 time, put the inoculate down. Does it survive? Does  
5 it proliferate? Or you can put the organism down,  
6 give it a running head start, and then come along and  
7 ask, can you get rid of it? Can you kill it, and how  
8 quickly can you kill it?

9 A lot of tests have used variations of the  
10 so called glove juice test, putting your hand in a  
11 sterile bag with a detergent solution to remove  
12 bacteria, particularly, as we were just discussing,  
13 developed many years ago for looking at immediate as  
14 well as persistent effects.

15 One of the things that we have emphasized  
16 is that, if you look in the literature starting back  
17 in the thirties with Price, who did it first, that  
18 when you use that kind of technique, no matter how  
19 many times you look, you keep getting lots and lots of  
20 bacteria. You keep getting millions of bacteria,  
21 which then led to theories that there were hidden foci  
22 of bacteria under the stratum corneum of the palm.

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1           We showed that, if you obliterate the nail  
2           space, the subungual space, and now do it that you  
3           get, with some variation, but eventually you get to  
4           the point where you have very little in the way of  
5           bacteria, and that the subungual space is an area that  
6           has an awful lot of bacteria in it.

7           Now that's real important. If the surgeon  
8           is going to operate on any of us and they have -- he ,  
9           or she has a glove on, you don't care whether bacteria  
10          that get in your body came from the fingernail --  
11          under the fingernail or whether it came from the hand  
12          surface; but if you're talking about people in homes  
13          or other situations where the hand surface is  
14          contaminated, using a technique which samples the hand  
15          surface as well as the subungual space, when one is  
16          talking about noncontaminants like e. coli or  
17          Serratia, but one is talking about other organisms  
18          that are chronically there, that may not be the best  
19          way of doing it because of this problem with the  
20          subungual space.

21                 We developed the technique of using this  
22          handprint which can then be digitized, and with image

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1 analysis you can quantify these colony forming units.  
2 Then if you look at that result versus what one gets  
3 in the glove juice test with the nail spaces  
4 obliterated, you get a very good correlation.

5 So one can then ask -- can do the  
6 experiment easier in terms of measuring the effect on  
7 surface flora.

8 I'll just conclude by showing you some ,  
9 pictures of what a detergent does. A detergent will  
10 remove bacteria, which then very quickly -- the  
11 survivors regenerate. If you have an antimicrobial  
12 substance in it, you'll do better, but some things do  
13 even better only.

14 Only those of you up close can see that  
15 there are some left here. Presumably, you would like  
16 to use this material, and just showing you some data  
17 on topical alcohol solutions.

18 So I would just conclude by saying there  
19 are a lot of people in nonmedical settings who have on  
20 their skin, as well as at times on their hands, a  
21 variety of organisms potentially harmful to themselves  
22 and others.

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1           There are lots of methods out there, some  
2           of which you've heard very briefly today, that can be  
3           adapted with proper attention to things like  
4           neutralization, and correlated with results such as  
5           this recent study in atopic dermatitis with some of  
6           these studies with methicillin resistant staph aureus,  
7           etcetera, that you've heard, that can then give you  
8           benchmarks.

9           Although it does this in the clinics, and  
10          it does this in these easier-to-do in terms of  
11          logistics and expense studies, there's a group  
12          correlation. Then these ought to be the standards.

13          Depending on what -- the criteria is  
14          whether it's persistence, immediate, quick kill, how  
15          long it lasts, etcetera, can easily be worked out; but  
16          the present recommendations will not do it.

17          Thank you.

18          CHAIRMAN BRASS: Thank you. Questions  
19          from the panel? Dr. Maki?

20          DR. MAKI: In your trial with dermatitis  
21          and the role of anti-infective agent, did the control  
22          group have the identical formulation applied,

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1 including the corticosteroid?

2 DR. LEYDEN: They had everything the same  
3 except no TCC.

4 DR. MAKI: No antiseptic, right.

5 DR. LEYDEN: Exactly.

6 DR. MAKI: Good.

7 CHAIRMAN BRASS: Dr. Tong.

8 DR. TONG: Dr. Leyden, in your experience,  
9 can you tell us some examples of health risk from  
10 excessive use of topical antiseptic agents like we're  
11 talking about here today?

12 DR. LEYDEN: Yes. I can say that easy.  
13 I don't think there are any real risks at all. The  
14 detergents' systems have gotten better and better. I  
15 mean, there's been a revolution in detergent systems  
16 over the last 15 years, and there are more and more  
17 skin friendly detergent systems.

18 Now there are individuals who, by the  
19 nature of their skin, are more vulnerable, and there  
20 are individuals who, because of their job, are  
21 washing. As Elaine pointed out, years ago -- I mean,  
22 there are people washing 50 times every eight hours,

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1 and one of the projects she did with us years ago was  
2 to show, if you do that with water, nothing, just  
3 water, that that's damaging to skin.

4 I mean, skin is well designed to resist  
5 irritation, but you can overwhelm anybody's skin if  
6 you work hard enough at it with just water. So the  
7 detergent systems have gotten better and better.

8 The antimicrobial -- I hear people say, ,  
9 well, you're exposed to all these chemicals, you know,  
10 these antimicrobial chemicals. Well, they're washed  
11 off, you know, and they really are not inherently  
12 injury producing substances.

13 The question of the overgrowth of other  
14 organisms which has periodically been raised -- I  
15 think it's been clearly settled that, in terms of the  
16 kinds of materials that are being used by people, that  
17 is just not an issue.

18 DR. TONG: Thank you.

19 DR. MCKINLEY-GRANT: I had actually two  
20 questions. What about the issue of resistance of  
21 bacteria, particularly staph aureus? Is there any  
22 evidence that --

1 DR. LEYDEN: Well, the question of  
2 resistance to these antimicrobial substances actually  
3 was the subject of a discussion a year ago or so, I  
4 think, here. To make a long day short, the  
5 conclusion, I think, of everybody involved was that  
6 resistance to these antimicrobial substances is not an  
7 issue now, but obviously should be continued to be  
8 monitored, and is far less likely to occur than the ,  
9 way it does to antibiotics because of the nature of  
10 how these agents work.

11 So that's been fairly thoroughly  
12 addressed, I think.

13 DR. McKINLEY-GRANT: The other question --  
14 Well, actually two. One, which was the material that  
15 was used to eradicate bacteria, that the hands were  
16 clear?

17 DR. LEYDEN: Oh, that last one?

18 DR. McKINLEY-GRANT: The last slide.

19 DR. LEYDEN: Yes. That's a product I will  
20 be introducing.

21 DR. McKINLEY-GRANT: Oh, okay.

22 DR. LEYDEN: No, no. That was a form of

1 chlorhexidine.

2 DR. MCKINLEY-GRANT: Okay. And the other  
3 question: The public, I think, is under the  
4 impression that a lot of the antimicrobials really  
5 work for viruses. I mean, they're using --

6 DR. LEYDEN: Many of them do.

7 DR. MCKINLEY-GRANT: Many of them do?

8 DR. LEYDEN: Yes.

9 DR. MCKINLEY-GRANT: Okay.

10 DR. LEYDEN: Many of them actually do.

11 DR. MCKINLEY-GRANT: Well, I guess we have  
12 to address that, too, at some point. I mean whether--

13 CHAIRMAN BRASS: Well, that goes under the  
14 spectrum of activity issue.

15 DR. MCKINLEY-GRANT: Yes.

16 DR. LEYDEN; Then eventually, what do you  
17 do to allow a claim? But many of them do -- actually  
18 do that. In fact, yesterday I was looking at some  
19 people in a clinical trial, and this one patient was -  
20 - You know, I couldn't get close enough to her to look  
21 at what I was trying to look at.

22 She says, I have the flu. I said, well,

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1 I got to look at you, and my nurse reached in her bag,  
2 pulled out an antimicrobial lotion and said, put this  
3 on your hands, I don't want you getting sick.

4 CHAIRMAN BRASS: If I could follow up a  
5 little bit on the last point you made -- I don't think  
6 there's any question that the panel believes in the  
7 germ theory of disease. I think that's not the issue.

8 I think the issue --

9 DR. LEYDEN: There are a lot of doctors  
10 who have embraced that theory.

11 CHAIRMAN BRASS: Rather, how to interpret  
12 the surrogate of bacterial counts in the context of a  
13 clinical efficacy. The paradigm you closed with  
14 suggests that, in fact, what we need are some  
15 classical clinical trials to anchor the surrogates  
16 before we can interpret the surrogates.

17 DR. LEYDEN: I think those trials -- those  
18 clinical experiences -- I don't know, you know --

19 CHAIRMAN BRASS: Well, clinical experience  
20 or clinical trial.

21 DR. LEYDEN: Classical emphasized,  
22 underlined, whatever that means -- I think there are,

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1 and maybe some would disagree we need more, but I  
2 think there are clinical experiences with a variety of  
3 antimicrobial substances in a variety of vehicles that  
4 have been shown to have clinical benefit.

5 Now the most difficult thing you could do  
6 that I could imagine is to show that a detergent based  
7 material would benefit atopic dermatitis, because  
8 detergents, as we know, irritate atopic dermatitis ,  
9 patients more easily than the rest.

10 That's been done now. That's been  
11 achieved. So you can say, well, that material at that  
12 concentration has this benefit. You heard about  
13 Triclosan and MSR, methicillin resistant staph aureus,  
14 I mean, etcetera, at a concentration.

15 So those things -- If we agree that those  
16 experiences are well done clinical studies, then that  
17 means they have benefit. So now we go into the  
18 models, if you will.

19 As I say, there are many, many models that  
20 lots of us have -- will argue passionately that this  
21 model is done a little better than that model, but  
22 there are lots of good models out there, and you can

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1 look with proper attention to details like  
2 neutralization, which has not been done -- you can  
3 look at the results in those models, and then, I  
4 think, make the correlations that, if this material  
5 works clinically and it does this in this model and it  
6 does this in this model, that maybe those are  
7 standards, that we should ask other things to at least  
8 reach that level before we feel comfortable that they  
9 will be useful in these situations -- is what I would  
10 say.

11 So I think there's a lot out there. I  
12 think you can only -- You know, you can always do  
13 more. I think the one thing -- there have been  
14 several discussions like this, and last year we had a  
15 two-day session. It was ironic that 30 percent of the  
16 people got food poisoning the night in between the two  
17 days, which was kind of neat that that should happen  
18 while we're discussing that issue.

19 Now you're getting down to like, well,  
20 what are we going to ask things to do. I think there  
21 may be a need to get people together who do these  
22 tests with people who are trying to decide which of

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1       them is best, along with other people who have  
2       experience in developing methods in general and making  
3       clinical efficacy judgments, and then come up with a  
4       blueprint of what you're going to do; because as I see  
5       it -- and I appreciate the difficulties that people in  
6       the FDA have when they came out with that.

7               They had to come out with something, and  
8       the best attempt, based on the input they had at that ,  
9       time, was a series of tests that nothing can pass. So  
10      I mean, obviously, something has to be done, or else  
11      we have to get rid of everything and just say there  
12      will be no antimicrobial substances, which means if  
13      you get operated on, good luck.

14             CHAIRMAN BRASS: Well, at some level that  
15      does become a question, because, one, if there are not  
16      sufficient data, that becomes the conclusion versus  
17      whether, as you've indicated, there are sufficient  
18      data to establish surrogacy or relative value of  
19      surrogacies of a 98 percent reduction on a palm versus  
20      2 logs in a glove kind of testing.

21             DR. LEYDEN: Yes. Well, I think, as far  
22      as I'm concerned, I would have no trouble. You know,

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1 if you put me in charge of this process, I'll take  
2 care of it. I have no problem.

3 Now I have to convince you who have not  
4 been involved in this to make you feel comfortable.  
5 You know, I appreciate that, too. So -- but I think  
6 there is enough information out there.

7 There have been lots of us in this room  
8 who have been involved in this now for over 25 years.  
9 The process was started in 1972. It was supposed to  
10 be a two-year process, and here we are, still talking  
11 about it, and we're still having some of the same  
12 conversations.

13 Meanwhile, more and more information has  
14 accumulated that, I think, makes at least those of us  
15 who have been involved in it from the beginning feel  
16 more and more comfortable that these things can be  
17 answered. But then there keeps being new players in  
18 terms of starting from scratch almost and trying to  
19 interpret what is reasonable.

20 CHAIRMAN BRASS: Other comments or  
21 questions?

22 Because of the time, unless Dr. Larson

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1 objects, I'd like to take a ten-minute break now, and  
2 then continue after the break with Dr. Larson. Ten  
3 minutes.

4 (Whereupon, the foregoing matter went off  
5 the record at 10:27 a.m. and went back on the record  
6 at 10:38 a.m.)

7 CHAIRMAN BRASS: Thank you very much. Our  
8 next speaker will be Dr. Elaine Larson, Dean of the ,  
9 Georgetown University School of Nursing, speaking to  
10 us on health care personnel use hand wash.

11 DR. LARSON: Ms. Lumpkins asked me to  
12 address the area of the health care personnel hand  
13 wash. She used that as an example this morning. So  
14 I'm not going to go over the usual ideal  
15 characteristics or definition of a hand wash, but I  
16 did want to really sort of run through some data as  
17 some examples of some of the unresolved issues that,  
18 I think, are still there.

19 Clearly, the issues have to do with  
20 efficacy testing, which we have talked about this  
21 morning, and I'm not going to talk about the specifics  
22 of the TFM, but I will end by talking about several

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1 general areas that I think are still of concern.

2 I want to talk a little bit about residual  
3 activity and whether it's really needed in a health  
4 care personnel hand wash, skin health and aesthetics,  
5 the idea of irritancy and what that means clinically,  
6 and give you some data, some of our recent data on the  
7 relationship between hand washing and irritant contact  
8 dermatitis in health care professionals, and then ,  
9 maybe a little bit about cost/benefit ratio.

10 I would like to make a comment about the  
11 question about randomized clinical trials and so  
12 forth. That would be lovely. We've actually tried a  
13 couple of times to start and done blinding and  
14 randomization and everything, and in every case we  
15 have been cursed with a variety of outbreaks and other  
16 things that go on in the clinical setting that have  
17 made it pretty much impossible to do.

18 I think there are a few people who might  
19 be able to pull it off, maybe Dr. Maki, but other than  
20 that, I don't know if we can do it.

21 This is just -- I went around the hospital  
22 one day and just picked up all the health care

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1 personnel hand wash products that were available in  
2 one hospital to show that we have a variety of things  
3 available, even in a single hospital.

4 Clearly -- Now this is from a housewife,  
5 and this is hand washing, pre- and post-hand washing -  
6 - do we have a pointer here? Obviously, the left is  
7 pre-hand washing, and post-hand washing with a plain  
8 soap. So there is, clearly, a reduction in transients ,  
9 with a plain soap.

10 Again, this is the same slide that Dr.  
11 Leyden showed from his group. I think he showed this  
12 slide. Clearly, efficacy -- and there is variation in  
13 products based on whether one is using a detergent  
14 base or a povidone iodine or chlorhexidine gluconate.  
15 These are just three different series of tests with  
16 ten subjects and a wash for three minutes.

17 Other ways that we've looked at efficacy  
18 over the years: This is a study that we did with a  
19 sample of 12 in each group randomly assigned to one of  
20 four products, a 70 percent ethyl alcohol, .5 percent  
21 chlorhexidine combination, povidone iodine CHG,  
22 Triclosan and always a control soap.

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1           This was a health care personnel hand wash  
2 protocol in terms of the -- It was a short hand wash,  
3 but we were looking at effect on resident flora. This  
4 is not the *Serratia marcescens* current health care  
5 personnel protocol.

6           These are the baseline results in log  
7 counts for each of the products, and you can see --  
8 now this is with immediate neutralization, and I would  
9 agree with the points that were made this morning,  
10 that perhaps some of these products are unlikely to  
11 meet the current standard in the monograph. This is  
12 after day one of 15 hand washes per day, and this is  
13 after day five. Again, this is reductions in  
14 colonizing flora.

15           Bottom line is that the alcohols performed  
16 the best. Povidone iodine was not very exciting at  
17 all. Chlorhexidine gluconate, even after five washes  
18 -- I mean, after 15 washes on the first day, was not  
19 very impressive. It was better after day five.

20           The Triclosan was not much different than  
21 the plain soap. Again, this is on colonizing flora,  
22 however. This is not a health care personnel hand

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1 wash protocol.

2 This is just bacterial regrowth in this  
3 same study four hours after scrubbing with a glove on.  
4 The point I want to make here is that, although the  
5 regrowth for the alcohol, which does not have a  
6 persistent or residual effect, was a little under half  
7 a log after four hours. It still hadn't reached  
8 baseline.

9 So I'm not really clear, if you have a  
10 very good agent, why you need the residual, because in  
11 fact, even after four hours without the persistent  
12 effect, the alcohol -- the counts on the alcohol  
13 treated hands were still lower after four hours than  
14 the counts with the other products.

15 We concluded that the bacterial counts  
16 following the alcohol scrub were significantly lower  
17 than the other products, and the significant  
18 reductions in counts were sustained even after four  
19 hours of gloving, and that's without any persistent  
20 effect.

21 Another point I wanted to make, moving on  
22 from efficacy, then from residual effect, to the

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1 differences in host characteristics and effect of  
2 products on skin. For example, these are some studies  
3 that we did with Jim Leyden's group in the 1980s,  
4 looking at differences in skin flora on the hands of  
5 physicians and nurses and other direct care providers  
6 on two different units. One was a bone marrow  
7 transplant unit, an oncology unit. The other was a  
8 dermatology outpatient unit.

9 The asterisks show the significant  
10 differences in skin flora. This is colonizing flora  
11 after hand washing, and our definition of colonizing  
12 flora required that they have the same isolate -- or  
13 the same organisms on their hands over a period of  
14 many months and a series of samples. It wasn't just  
15 a single culture. It was cultures over a 12-month  
16 period of time.

17 What we found is that, as you might  
18 expect, the dermatology personnel were reflecting some  
19 of the flora of the patients that they contact, as  
20 were the oncology personnel, 14 percent of whom had JK  
21 coryneforms -- that is, a multiply resistant  
22 diphtheroid -- on their skin.

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1           This is part of their colonizing flora.  
2       As you can see, three-fourths of the oncology staff  
3       were colonized with yeast, as compared with about one-  
4       fourth of the dermatology staff.

5           Further, just to show you a little bit  
6       more of this, this column here, the blue, is the same  
7       oncology staff. The second is the dermatology staff.  
8       The red line are patients who had been in the hospital ,  
9       for 30 days or more -- in those days they did that;  
10      this was in the late eighties -- and then the  
11      turquoise, last line, is a group of -- I believe in  
12      this case it was a sample of 25 controls, i.e., people  
13      who did not work in a hospital, who were not taking  
14      antibiotics and had not had any for at least the past  
15      month, secretaries, construction workers, etcetera.

16           This is the percent resistance of their  
17      staphylococcal flora, both their coagulase negative  
18      and positive flora, on -- in the case of the controls  
19      and the staff, it was their hands. In the case of the  
20      patients, it was actually on several body sites,  
21      including the hands.

22           The point of this -- and this is just some

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1 of the antibiotics that we tested these strains  
2 against. The point is that, for every antibiotic  
3 against which we tested, the oncology staff colonizing  
4 flora was significantly more resistant to every  
5 antibiotic we tested than of the dermatology staff or  
6 the patients, again, I think, reflecting -- and this  
7 was significantly correlated with frequency and  
8 intensity of touching of patients.

9 We know that this isn't from handling  
10 antibiotics, because pharmacy personnel do not have  
11 antibiotic resistant flora, but nurses and physicians  
12 in direct contact with patients do.

13 The whole point of this is that there is  
14 a constant exchange, clearly, between the patients and  
15 the hands of the health care personnel, and we have  
16 clear evidence now, not just from our work but from  
17 other people's work, including Dr. Maki's, that the  
18 hands of health care personnel can be reservoirs of  
19 antibiotic resistance.

20 Now what does this have to do with our  
21 conversation today? What it has to do with is that I  
22 think there are differences in the need for antiseptic

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1 products perhaps, depending on the level of risk or  
2 the kinds of exposures that people have.

3 The other thing that is different is that  
4 we have a number of host characteristics that may have  
5 an influence on a choice of an antiseptic. This is  
6 actually from a long time ago. This is my doctoral  
7 work in the 1970s, but the risk for colonization --  
8 again, colonization means on clean hands in a series  
9 of cultures, not once but over a period of months. So  
10 these are colonizing flora, not transient or  
11 contaminating flora.

12 What is the risk of being colonized with  
13 gram negative bacteria, and comparing hospital  
14 personnel and, again, a group of controls. In this  
15 case, the sample size was well over 1,000 individuals  
16 studied for over a year.

17 Men have a 4.5 times greater relative risk  
18 of being colonized for long periods of time with gram  
19 negative bacteria than women. Those who report  
20 washing their hands greater than eight times per  
21 working shift or eight times in an eight-hour period  
22 have a three times -- Those who report washing their

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1 hands less than eight times per shift have a three  
2 times greater relative risk of being colonized with  
3 gram negative bacteria, and individuals over 55 have  
4 a three and a half times greater risk of being  
5 colonized with gram negative bacteria as well.

6 Again, my point is that some of our  
7 titling of health care hand wash may be a misnomer,  
8 that there are lots of other things going on, and food ,  
9 handling, daycare providers, other folks may be in a  
10 similar risk category for some of these things as  
11 health care personnel.

12 I just wanted to end by talking a little  
13 bit, showing you some recent data from some studies  
14 that we've conducted on the effects of hand washing on  
15 the skin.

16 Let's see now. Oh, this is just a study  
17 that we did, because there are new products out there,  
18 these protectant lotions that have a dimethicone or  
19 some kind of a mechanical barrier as well. They may  
20 influence what we choose to select for antiseptics as  
21 well.

22 In this study, we were just looking at the

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1 effects of the use of a foam product on whether or not  
2 there were changes in the microbial counts. We have  
3 some evidence from clinical and lab data that these  
4 foam products, with or without an antimicrobial  
5 ingredient, may also reduce the transmission of  
6 microbes between people, probably by reducing skin  
7 claim shedding, but also by creating not just a  
8 chemical but an actual physical barrier.

9 This is a study that we did in the 1980s  
10 that compared -- Dr. Leyden mentioned this. This is  
11 the percent change in skin condition based on several  
12 measurement tools that we used. This happened to be  
13 the subject assessment. We also use transepidermal  
14 water loss and others.

15 We were able to show significant  
16 differences in skin condition, depending on what  
17 product was used. In this protocol it was 64 subjects  
18 who used a health care personnel hand wash protocol 24  
19 times a day for a week, and even with water we saw  
20 some skin damage. In fact, this was a regular bar  
21 soap. This happened to be a chlorhexidine gluconate.  
22 This was an iodophor. This was a second iodophor.

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1           We were able to show that, even in this  
2 fairly intense protocol of 24 washes a day for --  
3 under observation in the lab for a week, that some of  
4 the antiseptic products were, in fact, actually in  
5 this case better than the bar soaps, significantly  
6 better than the bar soap, and this antiseptic product  
7 containing povidone iodine was significantly worse.  
8 This one, in fact, never made it to market.

9           Here's some recent studies, one of which  
10 is published, and the second of which is in press,  
11 just to look at the effect of various -- to look at  
12 the correlations between hand washing practices and  
13 skin condition in a group of nurses.

14           In the first survey, basically, it was a  
15 prevalence survey to correlate skin damage on hands of  
16 nurses in four hospitals, two in this area and two in  
17 the northern U.S., actually in Ann Arbor, Michigan.  
18 We did it during the winter, because we were  
19 interested in whether we could sort out any effects of  
20 weather as well as hand washing.

21           We had 410 nurses in this study, all of  
22 whom worked essentially full time in acute care. We

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1 assessed skin damage with several techniques. We used  
2 a visual examination under a magnifying glass. We did  
3 self-reported questionnaires. We had a dermatologist  
4 consultant. We did a lot of psychometric work to make  
5 sure that we were getting reproducible results that  
6 were valid, etcetera.

7 We excluded all those with any diagnosed  
8 dermatologic problems such as eczema, atopic ,  
9 dermatitis, etcetera. These are just normal nurses  
10 working full time.

11 What we found is that, much to my  
12 surprise, about one-fourth of the nurses had  
13 measurable, current irritant contact dermatitis, much  
14 higher than I would have guessed.

15 Most of them reported that at some point  
16 in the immediate past they had had some serious  
17 problems with their skin, and the damage was not  
18 correlated in this study with age, sex. All but, you  
19 know, a few of them were women, and most of them were  
20 working age, between 22 and 45. So there wasn't a big  
21 spread in age; skin type, light skin, darker skin;  
22 soap use at home; duration of hand washing or glove

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1 brand.

2           These are the correlates of hand washing.  
3 The type of soap used at work was a significant  
4 predictor. Chlorhexidine gluconate containing  
5 products in this study, interestingly, was  
6 significantly less often associated with skin damage  
7 than using just a plain soap or a detergent, and the  
8 most damaging were the other antimicrobial detergent  
9 based products that were used, and in this case it was  
10 primarily a PCMX based product. So that was the one  
11 that had the most association with skin damage.

12           There was a significant correlation, as  
13 you would expect, with frequency of hand washing,  
14 frequency of gloving, and study site. When we did our  
15 logistic regression analysis, the independent  
16 correlates of skin damage that fell out after all  
17 these things were put into the equation were only two,  
18 the soap used at work and the frequency of gloving.

19           We did a follow-up survey that's now in  
20 press, and what we wanted to do here was to compare  
21 the microbial flora of hands of nurses with healthy  
22 and damaged skin to see is there a correlation between

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1 skin damage and skin microbiology.

2 So we took 20 of the subjects that had  
3 been identified in the first study with skin damage  
4 and 20 with healthy skin, and we looked -- we did  
5 prospectively now a look over a period of three  
6 months at their skin practices, their skin flora, and  
7 skin condition.

8 We did, as I said, a prospective data ,  
9 collection for three working weeks over a three-month  
10 time period. Subjects kept a detailed diary of their  
11 hand care, every time they washed they hands,  
12 etcetera. Skin condition was scored by the methods  
13 that we used before.

14 Hands were cultured with the usual gloved  
15 use technique after hand washing, immediately after  
16 hand washing, and we monitored by having -- We paid a  
17 couple of data collectors essentially full time to  
18 monitor compliance with the diary so that we were sure  
19 we were getting good, solid information on skin  
20 practices and hand washing practices.

21 Again, the microbiologic methods are  
22 exactly what you would expect. Some of the results:

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1 The mean hand washes per hour prospectively, as  
2 recorded as they're being done, was two. That means  
3 that somewhere between 15 and 30 hand washes per shift  
4 are occurring.

5 About half used a nonantimicrobial  
6 product. The mean glovings per hour was 1.3. Most of  
7 the nurses used powdered gloves only, and the vast  
8 majority used hand lotions, which is again a concern  
9 that I want to alert us to.

10 For example, in this study, as you see,  
11 essentially everyone but one, I think, used hand  
12 lotion. In every case, they were using a  
13 chlorhexidine gluconate product that was incompatible  
14 with the hand lotion that they were using. So that  
15 the hand lotion was neutralizing the effect of the  
16 CHG.

17 This is another consideration now for the  
18 use of antiseptic products. It's well known in the  
19 literature that, with CHG products, it's necessary to  
20 use non-ionic hand lotions rather than ionic, but the  
21 ubiquitous hand lotions in the hospital are anionic  
22 products.

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1           So, basically, health care workers are  
2           using an antiseptic product, thinking that they're  
3           getting the efficacy of an antiseptic, and  
4           neutralizing the results. So that's another big  
5           concern.

6           This is hard to read. There was no  
7           significant difference in the mean colony forming  
8           units on the undamaged hands -- the mean log was 5.63 ,  
9           -- or the damaged hands. So there was no difference  
10          in the quantity of flora among those with damaged  
11          hands. However, there were a larger of isolates per  
12          sample. So that per sample there were an average of  
13          about six on undamaged skin, eight with the damaged  
14          skin.

15          Our power, as you can imagine, because we  
16          only had 20 per group, was very low here. So my sense  
17          is that some of these nonsignificant results would  
18          have been significant if we had had a larger sample  
19          size.

20          In terms of the flora, twice as many  
21          nurses with damaged hand were colonized with staph  
22          homines. Don't ask me what that means clinically. As

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1 far as I know, it doesn't mean a lot except that staph  
2 homines is known to be associated with dry skin. So  
3 you would expect to see it more.

4 Then twice as many were colonized with  
5 staph aureus. Twice as many carried gram negative  
6 bacteria, enterococci and candida among the damaged  
7 group as compared to the undamaged.

8 In terms of comparisons with previous  
9 studies, these are just some of the studies that we've  
10 published over the years. A group in 1986 of oncology  
11 nurses, the mean colony forming unit over a period of  
12 about a year of colonizing flora was 4.79; in '92, a  
13 group in Peru, 5.74; and in this current study 5.61.

14 So there doesn't seem to be any  
15 significant change in the quantity of flora.  
16 Resistance to methicillin -- and you'll kind of have  
17 to follow through. The power point didn't come out  
18 the same as the slide, but in '86 with 50 isolates, 68  
19 percent were methicillin resistant. This is coagulase  
20 negative staph.

21 In '88, 81 isolates, 50 percent were  
22 resistant, etcetera, etcetera. The point again is

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1 that it does not appear that the resistance to  
2 methicillin among the staphylococcal flora of nurses  
3 is increasing.

4 Interestingly, the resistance to the flora  
5 to tetracycline was actually lower. In our current  
6 study only ten percent of isolates were resistant to  
7 tetracycline, as compared in the past with anywhere  
8 from 23 to 47 percent. No increase in antimicrobial  
9 resistance over the past decade.

10 What we concluded was that efforts to  
11 improve hand condition are warranted, because skin  
12 damage is associated with changes in the flora, and  
13 they're not in the right direction; that efforts  
14 should include monitoring of hand care practices,  
15 adoption of protectant products in policy protectants  
16 such as barrier creams, etcetera; increased use of  
17 powder free gloves; and so forth.

18 Now I do think that the adoption, which  
19 we're seeing now in clinical environments, of some of  
20 these protectant hand lotions may have a significant  
21 clinical effect on even perhaps the efficacy or,  
22 certainly, other attributes of some of these

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1 antiseptics, and may have some implications for our  
2 testing.

3 Let's have the lights, and I did want to  
4 just end by making a couple of comments about the  
5 monograph, as I was asked to make comments about  
6 perhaps some of the testing issues.

7 I'm not going to go over the monograph in  
8 detail, because I did it in 1994, and my stuff is  
9 there, just like hundreds of other people's were; but  
10 I wanted to make three comments.

11 First of all, the wash protocol for health  
12 care personnel hand wash, in my opinion, is not -- I'm  
13 now speaking as a clinician. It's not at all  
14 realistic. Nobody washes their hands for 30 seconds.  
15 If we can't test with the way the products are  
16 actually going to be used, and in fact that is outside  
17 label requirement -- I mean, that is outside  
18 directions on the label anyway.

19 So why don't we test products for the way  
20 they're actually used, which is ten to 15 seconds or  
21 not at all. Nobody washes their forearms 40 times a  
22 day. Why even bother to -- Those are just minor

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1 little things, and there are a lot of little things  
2 like that that really have an impact on the clinical  
3 relevance of the testing.

4 Second concern, major concern, is that the  
5 labelling section assumes that there will be health  
6 care personnel hand wash products used without water,  
7 i.e., alcohols, but the testing protocol doesn't  
8 address how you're going to test those at all.

9 So how can you assume -- What I read from  
10 that is there's an assumption of efficacy as a health  
11 care personnel hand wash, and yet there's no protocol  
12 to test it. I think that's a major problem.

13 I really fear that, while I've been one of  
14 many, many advocates for the need for controls and  
15 standardization, it just isn't quite the right balance  
16 between flexibility and clinical relevance and  
17 standardization. Somehow it doesn't quite meet it  
18 yet.

19 The main thing I'd like to say in  
20 conclusion, however, is I'd like to suggest that this  
21 whole titling of health care personnel hand wash  
22 products is outmoded and inappropriate, and we really

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1 need to rethink the whole thing for two reasons.

2 First of all, could we think about  
3 changing the definition away from a focus on the  
4 provider or the person, the user -- that is, the  
5 health care worker -- to the risk category; because it  
6 seems to me we've heard a lot of evidence, which I  
7 agree with, this morning that there are people,  
8 whether or not -- no matter what their work site, who ,  
9 are in need of using this kind of an antiseptic  
10 product.

11 Sometimes during outbreaks in daycare  
12 centers they ought to use it. Food handlers perhaps  
13 ought to be in the same category or certain types of  
14 food handlers, anybody who is working in an area where  
15 there's a high risk of contamination of the hands.

16 So my suggestion is that we -- I think  
17 we've made too many categories, and we've made it too  
18 complicated, and maybe we don't need food handlers  
19 antimicrobial wash -- Maybe we need that. I could  
20 argue there, but health care personnel hand wash. Why  
21 are they different than a daycare provider during an  
22 outbreak?

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1           You know, people are not in the hospital  
2           very long. The spectrum of care is so wide that  
3           you've got people who would have been caring for high  
4           risk people in a hospital now in the home, now in the  
5           long term care facility.

6           So I think we would be doing the  
7           marketplace a great favor if we got away from the  
8           focus on the user and focused rather on the risk ,  
9           situation, and made our title different.

10           The second area where I think it's a  
11           misnomer is the idea of wash. So it's health care  
12           personnel and hand wash. Obviously, we're talking  
13           about some products that you use with water and you  
14           wash, and some products that you use without water and  
15           they're not washes.

16           So the whole titling, I think, needs to be  
17           rethought. Thanks.

18           CHAIRMAN BRASS: Thank you. Questions,  
19           comments from the panel?

20           I have two questions. First, something  
21           you pointed out at the beginning that came up at an  
22           earlier presentation was the immediate versus delayed

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1 neutralization and impact on the testing.

2           Could you just clarify which is currently  
3 within the TFM standard, and which you think is the  
4 most relevant for testing?

5           DR. LARSON: Well, which is in the current  
6 standard? Delayed? Well, I don't know, but --

7           CHAIRMAN BRASS: I think it is delayed.

8           DR. LARSON: But we use immediate.

9           CHAIRMAN BRASS: And why is that?

10          DR. LARSON: For the same reasons that  
11 were discussed this morning, because in our -- Early -  
12 - and I started doing this in the 1960s and '70s, and  
13 the early stuff we did similar to that, and in fact we  
14 did publish a paper years ago -- I think it's from  
15 1968 -- to show that there was a significant  
16 difference if you used delayed or immediate; and I  
17 mean, also -- I have to say, this whole inoculation --  
18 As somebody mentioned, too, the Serratia on the hands,  
19 you can manipulate your testing within the TFM as it's  
20 written now in ways that can significantly change the  
21 results you get.

22          I have a real problem with that technique,

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1 because just by rubbing versus drying or just by the  
2 amount of pressure -- and we actually even published  
3 a paper on this. By the amount of pressure that you  
4 use when rubbing through the glove or the bag, you can  
5 make a significant difference in the numbers of  
6 organisms you get.

7 So it's an extremely, extremely touchy  
8 thing, and particularly when you're inoculating  
9 organisms on a living person.

10 I just want to say one other thing about  
11 my concern. We can't get the Serratia off when we're  
12 finished, and we stopped doing that technique, because  
13 our volunteers, we didn't feel, were safe. Even after  
14 four, six hours, soaking in alcohol, we still had  
15 Serratia marcescens on our hands, and we didn't feel  
16 like doing it anymore.

17 CHAIRMAN BRASS: Again, I understand  
18 there's a difference between immediate and delayed in  
19 the results, but which do you think is a more  
20 appropriate --

21 DR. LARSON: Immediate.

22 CHAIRMAN BRASS: -- for the clinical

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1 relevancy, if this is a surrogate test?

2 DR. LARSON: Immediate, because you're not  
3 -- What you want to do is test what's on the hand when  
4 you take it off.

5 CHAIRMAN BRASS: Okay. Thank you.

6 My second question goes to your last  
7 point, the expansion of the health care to other risk  
8 groups, and your points are well taken. But coming  
9 back to some of the issues the panel, I think, will be  
10 discussing the rest of the day is how comfortable are  
11 you in the surrogate marker of kill or decrease in  
12 colony counts, extrapolating from a health care  
13 validation model to other situations, and then all the  
14 way to the consumer use how do we use the surrogate  
15 across that spectrum?

16 DR. LARSON: Right. Well, of course,  
17 that's the bottom line question, isn't it, for all of  
18 us. I have to say, I was impressed with some of the  
19 risk modeling, and I thought in some ways that that  
20 may be a step between the kill, which -- the clinical  
21 relevance of that is iffy, in my mind.

22 You got to have it. It's necessary, but

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1 is it sufficient? I'm impressed with some of the  
2 modeling. I think that takes us a step further. I  
3 think that there's got to be a compromise between  
4 nothing, just depending on kill, and the randomized  
5 clinical trial for every single new agent that we're  
6 trying to put on the market.

7 So I would agree with some of the things  
8 that Jim said, that we have some evidence out there. I  
9 do think, however -- and that's one of the comments  
10 about cost/benefit -- I'm not sure that we have the  
11 evidence that for the general consumer use, but that's  
12 not what I was asked to talk about, which I didn't.

13 For general consumer use, what is the  
14 cost/benefit ratio? There is evidence with Triclosan  
15 that resistance does occur. As far as I know, there  
16 is no evidence that you can -- that the organisms can  
17 develop resistance to the alcohols.

18 So I don't have any concern about the  
19 alcohols. I think that there is a concern with  
20 antimicrobial resistance with ubiquitous use of these  
21 products by consumers over a period of years. I don't  
22 think that's resolved.

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1 CHAIRMAN BRASS: Thank you very much.

2 Our next speaker is Dr. Dennis Maki, Head  
3 of the Section of Infectious Diseases, University of  
4 Wisconsin Medical School, who will be talking about  
5 patient preoperative skin preparations.

6 DR. MAKI: When we consider enormous  
7 advances that have been made in health care in the  
8 last 30 years, I think it's quite astounding to many  
9 of our patients and the lay public at large that  
10 infection is still a serious problem, and the problem  
11 of institutionally acquired infection has become ever  
12 more complex over the last 20 years.

13 We've had a tremendous increase in  
14 antibiotic resistant hospitals. Nearly 50 percent of  
15 hospital acquired staph aureus infections now in  
16 hospitals over 500 beds are resistant to methicillin.  
17 We've lost the battle there.

18 Strains of enterococci resistant now to  
19 vancomycin and ampicillin pose us with the very first  
20 microorganisms that are resistant to all commercial  
21 anti-infectants, and we're using experimental drugs  
22 for therapy.

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1           Now I've been asked to address the issue  
2 of preoperative site care, and I also want to include  
3 in that the issue of vascular access. If we look at  
4 surgery, nearly 30 million patients undergo a surgical  
5 operation in this country every year. About two and  
6 half percent, based on this data, will develop a  
7 surgical site infection.

8           This translates to nearly three-quarters  
9 of a million surgical site infections a year in the  
10 United States. This is the second most common  
11 nosocomial infection. It's the most common infection  
12 in surgical patients, and it prolongs hospital stay  
13 seven days on the average, and adds at least \$3,000 to  
14 hospital charges.

15           This is the most sobering statistic.  
16 Three-quarters of all deaths in surgical patients in  
17 the hospital are related to a surgical site infection.

18           Now if we consider the issues that are  
19 involved in the genesis of a surgical site infection,  
20 obviously, the patient's immunity, the skill of the  
21 surgeon, but the bottom line is that most surgical  
22 wound infections are determined at the time that the

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1 patient is wheeled out of the operating room.

2 It is the number of microorganisms that  
3 have gained access to that wound intraoperatively, and  
4 if we simply look at stratifying types of surgery by  
5 the likelihood of intraoperative contamination by the  
6 patient's own flora, clean orthopedic or neurosurgical  
7 or cardiovascular procedures as contrasted with  
8 cutting across the stomach -- it has a modest flora --  
9 as opposed to cutting across the colon which has an  
10 enormous flora, the rate of infection is directly  
11 related to the likelihood of intraoperative  
12 contamination.

13 When we're talking about clean operations  
14 such as having a coronary bypass procedure, having a  
15 sternotomy, infections here are almost exclusively of  
16 staphylococci, skin staphylococci and, increasingly,  
17 coagulase negative staphylococci that are almost  
18 invariably resistant to methicillin.

19 It's quite sobering to realize the density  
20 of the cutaneous microflora. Dr. Leyden has really  
21 devoted his life to studying this area, and I think  
22 that some of his studies showing the ubiquity of

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1       staphylococcal       colonization       are       really       very  
2       impressive.

3               This is a study that we looked at cardiac  
4       surgery and cardiology patients, and we can get nearly  
5       4 logs of organisms off the anterior chest of a  
6       patient on admission to the hospital, culturing 25  
7       square Centimeters in a sterile template.

8               This remains absolutely stable throughout  
9       hospitalization. Now let's take the patient who goes  
10      to the operating room, has an open heart procedure.  
11      The day or two following surgery, there's been a  
12      significant reduction in the log numbers, but it's not  
13      that great a reduction in the log numbers,  
14      illustrating that all of these agents used to reduce  
15      counts of organisms on skin certainly don't sterilize  
16      the skin. All they do is reduce the number  
17      significantly.

18              Everything that we do in the operating  
19      room, the whole ritual of antisepsis, is designed to  
20      try to minimize the problem of access of organisms to  
21      the wound.

22              Now I'd like to say a few things about the

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1 other area that I think is encompassed by the  
2 preoperative site care part of the monograph, and that  
3 is vascular access for fusion therapy, administration  
4 of drugs, hemodynamic monitoring.

5 This is not a trivial issue, and it's  
6 become very complex, particularly the enormous  
7 increase in use of central devices of all types, not  
8 only temporary devices but increasingly long term and  
9 permanent devices such as cuffed Hickman or Broviac  
10 types of catheters or even subcutaneous ports that are  
11 now widely used in patients who need chemotherapy for  
12 cancer.

13 180 million intravascular devices of  
14 various types are sold to hospitals and clinics in  
15 this country every year. What we've learned over the  
16 last 20 years is that the single most important risk  
17 factor for developing a bacteremic infection with  
18 these devices is the type of device we put in.

19 The risk now is primarily with central  
20 devices of various types. By a variety of methods,  
21 you can project there's somewhere in the range of  
22 about a half million to a million device related

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1 bloodstream infections in this country every year.  
2 This is not a trivial problem.

3 If you look at the microbiologic profile  
4 of device related bloodstream infection, we find that  
5 coagulase negative staph candida and staph aureus  
6 account for probably two-thirds of all these  
7 infections. These are skin organisms. But if you do  
8 studies where you prospective look at the source of  
9 infection, do molecular subtyping between what you get  
10 from the bloodstream, what you culture off of the tip  
11 of the device or the hub of the device, what you'll  
12 find is that skin organisms account for probably two-  
13 thirds of all device related bloodstream infections,  
14 usually the patient's own flora.

15 In this study, large trial, heavy  
16 colonization at the insertion site was the single most  
17 important risk factor for a patient developing  
18 infection of the central venus catheter.

19 If we look at the differences in risks of  
20 infection with central venus catheters versus arterial  
21 catheters versus peripheral venus catheters, this is  
22 a study in a large coma unit. The risk of infection

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1 with peripheral venus catheters now is very low  
2 throughout the United States, probably one infection  
3 per 500 devices. With arterial catheters it's about  
4 one percent. With central lines it's about three to  
5 five percent in most centers.

6 If we look at the number of organisms on  
7 the site at the time we decide to prep it before  
8 insertion, the risk of infection is directly related ,  
9 to the number of organisms present. The number of  
10 organisms that are present on an internal jugular or  
11 subclavian access site is logs greater than we might  
12 have on the risk of the dorsum of the hand.

13 Moreover, it's much more likely that we're  
14 going to see gram negative rods, staph aureus,  
15 intracoccus or yeast.

16 Now with that background, let's talk about  
17 the monograph and critique -- I'll offer my critique.  
18 These are the definitions incorporated in the rule for  
19 a health care antiseptic or pre-op skin preparation  
20 drug product.

21 Here, I don't think that there's any  
22 question but that we would like something that's very

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1 broad spectrum, and I think that it's desirable that  
2 it be persistent. Whether we're talking about an  
3 operation that might last three hours or five hours or  
4 six hours or eight or ten hours, there will be grow-  
5 back. There is no question about it.

6 Suppressing grow-back certainly has to be  
7 desirable, because you're not going to stop the  
8 operation after three hours to re-prepare the edges of  
9 the wound.

10 When we're talking about an intravascular  
11 device, that device will stay in place for days,  
12 sometimes in terms of long term devices months, but  
13 certainly between site care, which may be as frequent  
14 as daily, more frequently now in most centers -- it's  
15 every second or third day; in an outpatient home care  
16 setting it might be once a week -- preventing grow-  
17 back is desirable, because grow-back does increase the  
18 risk of infection.

19 Now what are the professional guidelines  
20 of organizations as regards preoperative surgical site  
21 care and in terms of vascular access? Basically, we  
22 have two major guidelines that are available to us.

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1           Could somebody sharpen this for me? I  
2           can't really control the sharpness.

3           We have the guidelines of the American  
4           Operating Room Nurses Association and the HCPAC panel  
5           of the CDC. For surgical site preparation, they  
6           specify -- make specifications about hair removal.  
7           That doesn't bear on the guideline. The issue is the  
8           antiseptic.

9           ORNA really does not give much. It's  
10          very, very general, and it really doesn't give us much  
11          help except it says to be good. In terms of the CDC  
12          guideline, it specifies alcohol, chlorhexidine or a  
13          tincture of chlorhexidine or an iodoform.

14          In terms of vascular access, the CDC  
15          guideline which is widely subscribed to by centers in  
16          the United States and beyond, it specifies alcohol,  
17          povidone iodine or two percent tincture of iodine.  
18          They discourage the use of antibacterials which  
19          probably increase colonization by candida, but based  
20          on a single study suggest that a topical iodoform  
21          ointment might be desirable on hemodialysis catheters.

22          Now let's get to the proposed rule or the

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1 monograph. I would suggest that, if we look at the  
2 monograph in terms of in vitro susceptibility testing,  
3 which I think is desirable because there are  
4 differences between organisms, I can't see much point  
5 including these organisms: B. fragilis, hemophilus  
6 influenza, micrococcus luteus or streptococcus  
7 pneumoniae.

8 The likelihood that they would be ,  
9 pathogens with regard to a surgical site infection  
10 related to failure to cutaneous antisepsis is  
11 vanishingly small, and this simply adds cost and time.

12 Although there is no evidence that there  
13 are differences in vitro susceptibility between  
14 antibiotic resistant organisms and susceptible  
15 organisms, the data are rather limited that have  
16 examined that issue. Because of the tremendous  
17 importance of resistant staph and enterococcus, I  
18 think that these ought to be included in in vitro  
19 susceptibility assessments of new antiseptics.

20 I think an anaerobe, however, where  
21 failure of cutaneous disinfection has clearly resulted  
22 in infection is Clostridium, and I think that

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1 Clostridium -- it would be desirable to include this  
2 in assessments.

3 I would also suggest it might be  
4 desirable, if we're looking at antiseptic agents, for  
5 instance, to hand care, to look at antiviral activity  
6 for Herpes simplex and respiratory syncytial virus,  
7 two very important viruses that have been known to be  
8 spread widely within hospitals on the hands of health  
9 care workers.

10 In terms of in vitro time kill, I think  
11 that this is of some value, but it's very general. We  
12 should specify criteria, at least three to four logs  
13 in a minute.

14 Now in terms of in vivo testing and  
15 volunteers, I have a lot of reservations about this.  
16 I'm not very enthused about studying healthy  
17 volunteers. They're not the same as patients.  
18 Patients in hospitals might have 6 logs of candida on  
19 their chest. They might have huge numbers of gram  
20 negative rods, and studying healthy volunteers may not  
21 really give us the best insight as to the relative  
22 efficacy of one agent as compared with another.

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1 I think we should -- I would agree very  
2 much with prior discussants here that we need to  
3 examine the criteria in terms of in vitro tests for  
4 studies that are done in small numbers of patients  
5 looking at efficacy in terms of cutaneous  
6 disinfection.

7 This is what I think, on the other hand,  
8 is really needed. I'm, frankly, very disappointed how  
9 little good clinical data we have to guide us in what  
10 we should do.

11 You know, if one of us starts having chest  
12 pain on the way home this afternoon and they bring us  
13 into a center, and we are having an acute anterior  
14 myocardial infarction, unless there's a compelling  
15 contraindication, your physician is going to give you  
16 a thrombolytic. Why? Because NIH has probably spent  
17 \$100 million over the last ten years studying over  
18 50,000 patients in various trials of different  
19 thrombolytics to demonstrate there's a ten percent  
20 reduction in mortality if you use a thrombolytic as  
21 opposed to you don't.

22 Well, when we're talking about millions of

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1 serious infections, it's astounding how little good  
2 data we have in terms of clinical studies that have  
3 told us what is the best agent to use.

4 I think it's clear that for surgical site  
5 care you can use an iodoform. You can use  
6 chlorhexidine. You can use tincture of iodine. You  
7 can use alcohol. But what if one of them is ten  
8 percent better than the other, 15 percent.

9 Ten or 15 percent reduction in the risk of  
10 surgical infection using the best agent would  
11 translate to preventing probably 70-80,000 serious  
12 surgical site infections every year, and probably save  
13 several thousand lives.

14 It is possible to do these trials. Let me  
15 show an example, when I get back to my second point.

16 For vascular access we're starting to get  
17 some data to guide us what we maybe ought to be doing.  
18 If we look at cutaneous disinfection before you insert  
19 an intravascular device, what's used in most hospitals  
20 in the United States is an iodoform.

21 What's used throughout most of Europe and  
22 in Canada is chlorhexidine. Now there's lots of

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1 potential candidates for antiseptics. Most of these  
2 are not approved for the indication in the monograph.

3 This is a trial done simply looking at  
4 vascular access, looking at three agents, looking at  
5 the gold standard in the United States, iodophorus, as  
6 opposed to alcohol. That's very popular in Germany  
7 and Austria, and looking at chlorhexidine. That does  
8 well in studies.

9 This is a study where the effort was to  
10 look at preventing bacteremia, not looking at what  
11 removes organisms from skin more effectively. The  
12 bottom line is what protects patients from serious  
13 infection.

14 So patients admitted to a trauma unit who  
15 would need an arterial line or central venous catheter  
16 were randomized at the time of catheter insertion.  
17 Now it was also rather interesting. The study showed  
18 that povidone iodine and alcohol were equivalent, with  
19 about a three percent rate of bacteremia.  
20 Chlorhexidine was fivefold better.

21 If these data are valid, which I'll show  
22 you data to think they are, switching to chlorhexidine

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1 tomorrow on a wide scale in U.S. hospitals would  
2 prevent hundreds of thousands of bacteremias in the  
3 first year.

4 Most catheters are put in by the Selvinger  
5 technique using a guide wire. This can introduce  
6 organisms into the lumen of the catheter. In this  
7 study it was possible to demonstrate that the superior  
8 antiseptic also prevented infections that were  
9 lumenally -- intralumenally acquired.

10 Here's a similar study in Europe looking  
11 at ten percent povidone iodine against a very low  
12 concentration of chlorhexidine and a low concentration  
13 of alcohol. I would be very nervous about using this  
14 agent, frankly, because of the low concentrations of  
15 the antiseptics, but again here the harponics are  
16 being performed well.

17 It reduced the incidence of gram positive  
18 bloodstream infection 80 percent. This is not the  
19 greatest trial, but it gives a trend, which I think is  
20 worthy of looking at, and that is it's a large  
21 nutritional support program in Europe where they use  
22 tincture of iodine exclusively for site care and

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1 disinfection for about three years. They then switch  
2 to an iodoform.

3           They realized they had a twofold increase  
4 in invasive infections in the population. They  
5 switched back to tincture of iodine, then to  
6 chlorhexidine, and came back to their lower level.  
7 This is not real strong data, but it's a trend that  
8 suggests that chlorhexidine and perhaps tincture of  
9 iodine is superior to iodoforms.

10           The last study I'll show is a multi-center  
11 trial done in neonates where peripheral venous  
12 catheters are used for access, looking at a tincture  
13 of chlorhexidine versus povidone iodine. Again, the  
14 chlorhexidine performed superiorly.

15           I think it's time that chlorhexidine,  
16 whether it's an aqueous solution or a tincture, be  
17 approved for vascular access in this country. This is  
18 not encompassed in the monograph, but I think it is  
19 such an important issue in health care, it bears strong  
20 consideration.

21           Dr. Larson could have probably given every  
22 presentation here today with the extent of the work

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1 that she's done on skin disinfection. This is a  
2 summary of studies that she analyzed in a recent paper  
3 that she published that looked at the efficacy of  
4 preoperative patient bathing, which bears on our  
5 issues today.

6 We don't have an answer as to whether  
7 preoperative bathing makes a difference or not. The  
8 major reason is that there have been four trials that  
9 have had infection as the endpoint of comparison.  
10 Unfortunately, two of them showed a significant  
11 decrease. Two of them did not.

12 On the other hand, there were methodologic  
13 differences in definition of infection, the number of  
14 preoperative showers that were used, and the answers  
15 is unresolved. Yet it is recommended, and most  
16 surgeons do use a preoperative antiseptic shower or  
17 bath before elected surgery.

18 We should get better data than this to  
19 tell us what should we use, what's the best way to do  
20 it.

21 If we look at surgical site preparations,  
22 the situation is even worse. There have been very few

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1 studies that have adequate statistical power to give  
2 us any insight as to the relative efficacy of the  
3 different agents that are currently approved for  
4 surgical site disinfection in surgery.

5 Most of the studies have looked at  
6 colonization. They have not used infection as an  
7 endpoint, and there is an awful lot more serious  
8 surgical infections and device related bacteremias  
9 than there are in myocardial infarctions. We ought to  
10 have better data than this.

11 Antiseptics, I would close by suggesting,  
12 have the greatest hope for being able to materially  
13 reduce the problem of antibiotic resistant organisms.  
14 Incorporating antiseptics into the device itself holds  
15 a promise of substantially reducing the risk of device  
16 related bloodstream infection.

17 The challenge is finding the best agents  
18 and, particularly, defining where they ought to be  
19 used.

20 Thank you very much.

21 CHAIRMAN BRASS: Thank you. Comments,  
22 questions from the panel? Dr. D'Agostino?

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1 DR. D'AGOSTINO: Could I just try to  
2 follow up on an idea of the clinical trial. If you  
3 think of the drug approval process, it might be  
4 different than the scenarios that you were suggesting  
5 where you were making comparative trials.

6 If you had a drug -- If we suggested, for  
7 example, or the panel suggested that the clinical  
8 trials really be looked at very seriously for  
9 approval, then you wouldn't do a placebo control,  
10 obviously.

11 Is there some standard that could be used  
12 for controls to make the comparisons for the approval?

13 DR. MAKI: I anticipated that question.

14 DR. D'AGOSTINO: Good.

15 DR. MAKI: And I thought about it. First  
16 of all, I don't think that it's going to be practical  
17 or as desirable for the panel to -- if they decide  
18 clinical trials are important, to decide that every  
19 manufacturer of the agents that are currently approved  
20 has to do clinical trials to show they're efficacious.

21 I think it's clear that the agents that  
22 are used do confer benefit, and they're going to be

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1 superior to placebo. There's no role for placebo  
2 controlled trials here.

3 There might be for preoperative bathing.  
4 That's another issue, but for surgical site care for  
5 vascular access that's not an issue.

6 What I would suggest, on the other hand,  
7 is that, if there's a promising new agent that wants  
8 to get into the market for surgical site preparation  
9 or for vascular access, it ought to have to have a  
10 good clinical trial, a clinical trial that compares  
11 with one or more of the currently approved agents.

12 If it turns out that the clinical trial  
13 suggests that the new agent is superior, I can assure  
14 you that it's going to prompt further studies of the  
15 older agents in the marketplace to try and defend  
16 their position in the marketplace; but I think that  
17 new agents -- and we certainly need new agents --  
18 ought to require clinical trials comparing with  
19 existing agents.

20 CHAIRMAN BRASS: Thank you. Other  
21 questions or comments? Thank you very much, Dr. Maki.

22 Our next speaker is Mr. John Guzewich from

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1 the Food Safety Initiative at the FDA, who will be  
2 speaking on food handler hand wash.

3 MR. GUZEWICH: Good morning. My name is  
4 Jack Guzewich. I work for the Food and Drug  
5 Administration in the Food Safety Initiative part of  
6 the Center for Food Safety and Applied Nutrition.  
7 I've worked there for 13 months.

8 Prior to that I worked for the New York  
9 State Health Department for 27 years where I ran the  
10 food borne disease epidemiology program and the retail  
11 food program, which is regulations over restaurants  
12 and supermarkets and the like.

13 I also want to comment before I begin that  
14 I do not take credit for talking about food borne  
15 disease just before the lunch period. I was not the  
16 scheduled designer for that little apparent piece of  
17 time in there.

18 What I want to talk about today is our  
19 concerns related to this -- See, I had food worker  
20 hand wash. You'll learn as I go along here that I  
21 have a particular problem with food handler. It's a  
22 big concern of mine. I've been a crusader for many

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1 years.

2 Can I have the next slide, please?

3 We have to begin on this by looking at the  
4 role that food workers, not handlers, have in the  
5 epidemiology of food borne disease. Evidence is  
6 becoming more and more strong that food workers are  
7 probably the -- that's with a capital T -- The major  
8 cause of contamination of food in restaurants and  
9 other places, rather than the raw animal foods and  
10 other things that are sort of dogma in that area.

11 So I want to talk a little bit about  
12 agents, and also about contributing factors, and I'd  
13 like to point out here that agents I consider all  
14 these three categories: The bacteria, the viruses and  
15 the protozoan parasites.

16 Most education in this area will make you  
17 think that bacteria are the major agents of concern,  
18 and there's a lot of biases into what has been  
19 reported in the past to lead you to that conclusion,  
20 but in fact viruses cause far more food borne illness  
21 than do bacteria, although not as severe disease.

22 We're now seeing -- the early stages are

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1 telling us that probably protozoan parasites are also  
2 being spread this way, and they will create all kinds  
3 of problems in terms of efficacy, if we're going to  
4 talk about trying to control them on hands.

5 I'll talk a little bit about the  
6 contributing factors that lead to food borne  
7 outbreaks, the causes that have our concerns.

8 First we'll take a quick look at some CDC  
9 data, and these are data that were compiled by CDC  
10 through a passive surveillance program. I emphasize  
11 that, because we could spend the rest of the day  
12 talking about the number of biases in this data.

13 Nevertheless, the way they categorize this  
14 information, you can see that there are -- On the  
15 lefthand side of these two tables, the contributing  
16 factors are what was felt by investigators to be the  
17 errors or the steps that led to this particular food  
18 borne illness.

19 For bacterial agents, you can see, for  
20 instance, that temperature in the 73-87 area was --  
21 temperature abuse was involved in 87 percent of the  
22 outbreaks.

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1 Well, if we go down to this one called  
2 hygiene, which is the fifth one down there, you can  
3 see there hygiene. Now hygiene covers a whole range  
4 of sins, not all of which are relevant to the day, but  
5 they all tie in, were involved in 59 percent of the  
6 bacterial outbreaks, 92 percent of the viral, 60  
7 percent of the parasitic and two percent of the  
8 chemical; and we get some kind of crazy insights into  
9 what all that means.

10 Then in the more recent period, '88 to  
11 '92, we had 34 percent of bacterial, 87 percent of  
12 viral, 33 percent of parasitic, and one percent of  
13 chemical. So hygiene is a major factor, obviously, in  
14 the way they categorize the data.

15 Now when I was in New York, we developed  
16 a system that we felt was a whole lot better than  
17 that, and we did report 33 percent of the food borne  
18 illness in the country, although we had only seven  
19 percent of the population in the States. That's not  
20 because food is that much more unsafe in New York.  
21 It's only because we cared to look for what was  
22 causing the problems.

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1                   Could I have the next slide, please?

2                   We get here our way of categorizing the  
3 data. We have some biases in here, too. We are  
4 particularly plagued with outbreaks associated with  
5 raw shellfish and with shell eggs, and those data kind  
6 of skew what's up here so that you see they're  
7 contaminated ingredients, which relates to many of our  
8 shellfish outbreaks and our egg outbreaks.

9                   Consumption of raw or lightly heated  
10 animal food: Again, there's a bias because of those  
11 kind of outbreaks.

12                  We go down here to infected person, and  
13 you can see infected person ranks five on that list;  
14 but if we took out the egg and shellfish outbreaks,  
15 infected personnel would become one of the major  
16 contributing factors to the food borne illnesses we  
17 saw over that 16 year period.

18                  Could I have the next slide, please?

19                  If we look at the agents that were  
20 involved in those outbreaks, you can see that  
21 nonspecific viral gastroenteritis -- and for those of  
22 you who are familiar with this phenomenon, you know

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1 that there's not readily available laboratory testing  
2 for the Norwalk family, and so you end up with these  
3 different euphemisms for what that disease is.

4 Anyway, that was the predominant agent in  
5 our food worker associated outbreaks, and salmonella  
6 was second. There you see we had some enteritidis,  
7 which people think are just with eggs, but we do get  
8 them food workers, too.

9 Then salmonella typhae: We had a  
10 beautiful typhae we could talk about. Hepatitis A,  
11 Norwalk virus, rotavirus. Could we over to the next  
12 slide, please?

13 Staph aureus, the one that's near and dear  
14 to everybody's heart; Shigella, Beta hemolytic  
15 streptococcus was involved in three outbreaks;  
16 Campylobacter in one, and Yersinia in one, 27  
17 outbreaks.

18 We had ill food workers involved, but we  
19 were not able to identify what agent they actually had  
20 anymore specifically than that. So you can see, we  
21 have a host of agents, both bacterial and viral.

22 We have no parasitic ones on there. We

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1 didn't have that experience, but I can tell you just  
2 in my brief time here at CDC, I've been involved in  
3 two investigations here in the U.S. where we have  
4 reason to believe that food workers were involved.

5 One parasitic outbreak was cyclospora, and  
6 the other was cryptosporidium, and I'm sure that we're  
7 going to see more of that as time goes on. Next  
8 slide, please.

9 So the role of food workers in food borne  
10 disease is quite significant, and I'm just talking now  
11 about the agents that the worker carries when he or  
12 she walks into the job in the morning. I'm not  
13 talking about the ones that they pick up from the raw  
14 chicken and transfer over to the ready-to-eat food.  
15 I'm talking about the ones that are carrying in or on  
16 their bodies.

17 We think that is a major source. Our  
18 problem in this industry is that people work when  
19 they're ill. They don't get paid if they don't come  
20 to work. They may, in fact, lose their jobs if they  
21 don't come to work. So our economic incentives are  
22 come to work, even though you're ill, and in fact,

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1 that's what they do.

2 So they're going to be there when they're  
3 not feeling well, not to mention when they're in some  
4 kind of a carrier state. Added to that is the problem  
5 that people do not wash their hands. Food workers are  
6 not unique in this respect and, when they do wash  
7 their hands, they don't do it very well.

8 You didn't know, but we had the hands  
9 police in the bathroom this morning, but I did one of  
10 my usual informal, unofficial surveys, and found that  
11 even among people who sell these products and foster  
12 their use, hand washing is intermittent and certainly  
13 not in the duration adequate to achieve what we're all  
14 trying to achieve today. This is only in the men's  
15 room. I can't speak for the women's room experience  
16 in that regard, but I suspect it wasn't a lot  
17 different.

18 So people don't wash their hands, and  
19 that's a real problem for us. Could we go on to the  
20 next slide, please?

21 So what is the answer that the Federal  
22 government has to the world's problems? Well, in this

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1 area the FDA does have regulations over  
2 establishments, companies that prepare food that are  
3 sold in interstate commerce, and we have good  
4 manufacturing practices and the like.

5 We also have a document that we don't  
6 particularly enforce in most settings, but is a model.  
7 It's called the Food Code, and some of you have heard  
8 of this document and some of you haven't. But it's a  
9 model regulation that we encourage state and local  
10 regulatory agencies to adopt and enforce for  
11 regulating restaurants and supermarkets and similar  
12 kinds of establishments. Health care facility  
13 kitchens are included in that, by the way.

14 So that pertains to what we call retail  
15 food, and there are provisions in here that are  
16 relevant to the discussions today. One of them is  
17 that we say that people may not contact ready-to-eat  
18 food with their bare hands.

19 We've gotten to the point in this issue  
20 that we feel -- that was based on our experience in  
21 New York state when I was there -- that people are not  
22 going to do this the way it needs to be done. So if

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1 we can keep their hands off the food altogether, the  
2 ready-to-eat food, that's probably the most effective  
3 intervention.

4 Unfortunately, this intervention isn't  
5 agreed to by all parties, as you can imagine, and so  
6 in many places in the country, in fact most places in  
7 the country, that standard does not apply, because  
8 this is a voluntary standard.

9 So there's going to continue to be a  
10 legitimate need for hand wash products and sanitizing  
11 products that keep people's hands clean, even if this  
12 was in effect, and I'm sure it will never be in effect  
13 in all places.

14 The regulation requires that people's  
15 hands be in a clean condition, that they use a  
16 cleaning procedure, and we heard earlier about a 30  
17 second procedure. Our Code talks about a 20 second  
18 procedure. So if you're going to test these products,  
19 obviously, you've got to test them for a duration  
20 that's relevant to what's actually being required.

21 We tell them when to wash, and we define  
22 all the times when hands would be contaminated as to

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1 when to wash. We talk about where they should wash  
2 them, meaning a hand washing sink as opposed to the  
3 sink above where they are washing off the lettuce or  
4 something, and we talk about hand sanitizers.

5 Hand sanitizers are important in here,  
6 because we say that hand sanitizers should be used on  
7 clean hands. There are products in the marketplace  
8 today that are purporting to be used anytime you need  
9 to use them periodically, and we have retail  
10 establishments that have people periodically applying  
11 these compounds when they haven't got time to wash  
12 their hands.

13 Well, if they haven't washed their hands  
14 to remove the soil, then they negate what we say in  
15 our regulation. I'm sure most of you would agree  
16 with, that if you don't have a clean area to sanitize,  
17 then sanitizing isn't going to do you a whole lot of  
18 good.

19 If I can have the next slide, please.

20 We have some other concerns in this area,  
21 and I sort of alluded to some of them already. First  
22 is emerging pathogens.

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1           Emerging gets to be kind of a word,  
2           whichever fits, but some people consider viruses to be  
3           emerging pathogens. I don't really think they're  
4           emerging. They're just maybe not being recognized by  
5           everybody for a long time, and I don't know how we  
6           address viruses here.

7           We've heard already this morning by some  
8           of the scientists that these agents, cleaning agents  
9           and sanitizing agents, may have effect on viruses.  
10          Whether they will affect all these enteric viruses or  
11          not, I don't know. What effect they have on parasites  
12          may be even more problematic, and we are seeing the  
13          pathogens coming along with some characteristics that  
14          cause us some real concern.

15          E. coli 015787 is an organism that is  
16          particularly acid resistant. Now our microbiologists,  
17          when I discussed this testimony today, said, you know,  
18          we're not really sure whether this acid resistance is  
19          in anyway related to more resistance to sanitizers or  
20          not, but it's a concern of theirs.

21          There's a bug out there right now called  
22          Salmonella typhaemurium DT104 that is a multiply drug

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1 resistant salmonella that causes infection in animals  
2 as well as in humans, and an organism like that that  
3 is multiply drug resistant to antibiotics -- whether  
4 that relates to hand sanitizers, we don't know.

5 So emerging pathogens are a concern, and  
6 they're going to complicate the whole spectrum of this  
7 subject.

8 Also we have food additive requirements,  
9 and I'm going to allude to some of these things more  
10 than once. We have requirements in the FDA that  
11 things that are going to be in contact with food have  
12 to meet food additive requirements.

13 Well, that includes hands. So these  
14 sanitizing compounds that are on people's hands in  
15 theory can be transferred to the food. Therefore,  
16 they become food additives. Therefore, they have to  
17 comply with food additive requirements and concerns as  
18 well as all the others, and let me tell you, that's  
19 going to make life a little more complicated.

20 Next slide, please.

21 Attributes: Speed of action -- As I  
22 mentioned a minute ago, our regulation talks about 20

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1 seconds, which is what we recommend as the duration.  
2 Those of you who don't want to use a stopwatch, one  
3 stanza of "Old MacDonald" works very well to get you  
4 to about 20 seconds. You can try that the next time  
5 you're in the restroom.

6 Indicators versus pathogens: Our  
7 microbiologists are a little bit concerned about this  
8 one. We know that there's a lot of very good reasons  
9 why you want to use indicators rather than the actual  
10 pathogens, and those are certainly important reasons.

11 We're not sure that there's enough  
12 information there to show that you can always have an  
13 indicator necessarily truly represent what the  
14 pathogen is going to be like. So we're going to have  
15 to have some way of having confidence that the  
16 indicator represents all our concerns about the  
17 pathogen before we can make that leap of faith.

18 Then we have low dose agents. From the  
19 information I've seen today and information I saw at  
20 a meeting that CDER held last week, these agents  
21 typically are expected to reduce the loads on hands  
22 maybe by one log or two logs of organisms.

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1           We have a real problem here.   Some of  
2   these agents we deal with in food borne disease are  
3   low infectious dose organisms, and salmonella typhae  
4   fits in that category.   E. coli 0157 probably has  
5   infectious dose of ten organisms or less.   Coli is  
6   down there.   Shigella is down there.   The viral agents  
7   are down in that area.

8           So we have agents where you don't have to  
9   have a whole lot of them on your hands to make people  
10   sick.   So it gets real complicated what kind of claims  
11   we can make about these products in light of those low  
12   dose organisms.

13           Next slide, please.

14           Attributes:   Well, we have, first of all,  
15   spectrum of action, and what kind of claims can be  
16   made about organisms, the organisms concerned?   Are  
17   they the bacteria, the viruses, the parasites?   What  
18   do we say about those kind of things?   What kind of  
19   claims can we make about addressing all those  
20   different organisms of concern?

21           Then we have this resistance idea that  
22   I've already talked about.   Will these organisms show

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1 resistance? Will the more emerging pathogens, in  
2 particular, be a concern when they have acid  
3 resistance, when they have multiply drug resistance  
4 already being demonstrated?

5 Next slide.

6 Length of action: Does persistence, which  
7 is a great characteristic on these products, also make  
8 them more likely to be a food additive issue? I  
9 suspect -- I don't know. I suspect in some cases  
10 those may be working at cross-purposes, and that issue  
11 is going to have to be addressed if persistence, by  
12 its very nature, means you go into the food additive  
13 requirements.

14 Next slide, please.

15 The last slide I have is on the issue of  
16 soil, and I think that this gets real complicated.  
17 Soils that occur at the retail level are likely to  
18 also show up at the processor level. I don't think  
19 that you can necessarily say that people who are  
20 working in the processor's situation are necessarily  
21 going to have hands that are anymore soiled than you  
22 have at the retail level, because these days retail

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1 level does everything that goes on at the processor.

2 They're doing the whole spectrum of  
3 activity there. Also, you've got to -- I don't have  
4 it right here on the slide, but we also have to worry  
5 about a category that I haven't heard addressed yet  
6 today, and that's in the agricultural environment.

7 We have veterinarians who use hand wash  
8 products. We have other workers. We have people that  
9 work in milk houses that use hand wash products and  
10 then milk cows.

11 Also now, those of you who like to eat  
12 produce, and that would be some people in the room who  
13 do that, maybe are aware of our big concern in FDA  
14 about food borne illness associated with produce. We  
15 don't really know where the produce is becoming  
16 contaminated.

17 One of the possible sources is the  
18 agricultural workers in the field, and do they wash  
19 their hands or not; and if so, what do they use to  
20 wash their hands with and sanitize their hands with  
21 before they pick that produce that you may or may not  
22 cook before you eat?

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1 With all those troubling thoughts, I'll be  
2 happy to answer any questions.

3 CHAIRMAN BRASS: Thank you very much.  
4 Questions or comments from the panel? Dr. Maki?

5 DR. MAKI: An observation and a question.

6 First of all, to open the enormous barrel  
7 of worms of considering cutaneous antiseptics used on  
8 hands as an additive, then you better start getting  
9 ready to do that with all cosmetics and every other  
10 thing that you put on people's skin that people get on  
11 their hands, and they feed themselves. They use their  
12 hands to feed themselves.

13 I think that that's opening a huge pile of  
14 pain that may not be justified.

15 MR. GUZEWICH; I hear your point. All I  
16 can respond to is that it's --I mean, it's a fact.  
17 The food additive requirements have to be applied in  
18 these areas, and cosmetics -- I think those issues are  
19 addressed to some extent, but when you come out with  
20 a product that's specifically designed to be put in  
21 contact with a person's hand who in turn is going to  
22 be preparing food, you've opened yourself up to the

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1 food additive regulations.

2 When you're talking about a cosmetic that  
3 has that more indirect relationship, I'm not sure that  
4 food additive requirement applies, but it will apply  
5 in these situations, and I know it's going to  
6 complicate the issue.

7 DR. MAKI: And you're talking about hand  
8 lotions and all kinds of skin care products.

9 The question is: I've come to sort of  
10 look at the hands, the skin of the hands, as being a  
11 big sponge, and it attracts organisms, and once you  
12 put them on, exactly as Elaine pointed out, I think,  
13 you know, contaminating hands with Serratia is very  
14 artificial.

15 I'm not sure it tells us very much, and I  
16 agree completely. Why should you colonize a small set  
17 of the people permanently with a virulent gram  
18 negative rod if they're going to be health care  
19 workers someday.

20 The question is why not require all health  
21 care workers to use disposable gloves? I would think  
22 that that would be the logical way of making it

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1 convenient to eliminate this issue of organisms they  
2 may have in their hands, because they're incubating  
3 hepatitis A and they have ten million virions on their  
4 hands that you're not going to remove with a three-  
5 minute hand washing, but gloves, I think, might have  
6 the greatest hope for preventing food borne illness.

7 MR. GUZEWICH: You and I are of like mind  
8 on that, but that is not a universally held belief. '  
9 people don't like to wear gloves. They see a lot of  
10 objections to gloves. They feel they should have the  
11 right to have an effective hand wash in lieu of.

12 That's a very hotly debated area in the  
13 area of food safety right now, is whether prohibiting  
14 bare hand contact, which oftentimes relates to using  
15 gloves, although we out in the lobby use deli papers,  
16 tongs, spatulas. There's many things you can use  
17 other than your hands to do certain activities, but  
18 there are activities that, practically speaking,  
19 you're going to want that hand tactile aspect, and  
20 gloves are going to be involved.

21 We had this requirement in New York. We  
22 adopted it in '92. We've had a heck of a time getting

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1 compliance with that, but I can tell you -- and I'm  
2 involved in a bunch of epidemiologic work on this  
3 right now -- that there continue to be food borne  
4 outbreaks in the United States associated with ill  
5 workers who have bare hand contact with food.

6 In our tracing these things, we did not  
7 have outbreaks in situations where people were not  
8 touching the food and they were wearing gloves. It's  
9 that simple.

10 Now one of the things that's thrown back  
11 at us that you health care people know much more about  
12 than we do in the food area is that, when you have a  
13 glove on for a long period of time, you've got all  
14 kinds of things going on underneath that glove, too.

15 These are all the issues that you deal  
16 with in the health care saying that we're being thrown  
17 the same ones in the food sector. The difference is  
18 there are tomes' worth of studies that have been done  
19 on this in the health care setting.

20 As was brought up earlier, how much of  
21 that can be related over to the food setting? Is it  
22 appropriate to relate those over? Are they the same

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1 agents? Are they appropriate to be thought of in the  
2 same way? We don't have all those answers right now.

3 CHAIRMAN BRASS: Dr. Larson.

4 DR. LARSON: What's the rationale for the  
5 20 second hand wash, and what's the evidence of  
6 compliance with that? Do people really do that?

7 MR. GUZEWICH: I'm not sure whether -- I  
8 could find out for you where the rationale --

9 DR. LARSON: I mean, it's more stringent  
10 than health care workers, and I understand, you know,  
11 that they ought to be stringent, but --

12 MR. GUZEWICH: I don't know the answer to  
13 where that 20 second -- I could look that up for you.

14 As far as compliance, we have ample  
15 anecdotal evidence to suggest that compliance is not  
16 very high, and that's our problem.

17 DR. MAKI: See, where it's probably  
18 important for the food worker, more important than  
19 anything, is that they wash their hands really  
20 vigorously after they go to the bathroom.

21 MR. GUZEWICH; Absolutely.

22 DR. MAKI: We've studied organisms on the

1 hands of health care workers and non-health care  
2 workers, and it's very interesting. They both carry  
3 about the same amount of staph aureus.

4 The health care workers carry lots of  
5 methicillin resistant staph epi. which we virtually  
6 never find on the hands of non-health care workers,  
7 but when you look at the gram negative rods, the total  
8 log count of gram negative rods are about the same in  
9 both groups.

10 In the health care workers there's  
11 Kebsiellae, interbactus, Serratias, pseudomonas or  
12 hospital resistant gram negative rods. In the non-  
13 health care workers we almost never see those  
14 organisms unless they have a job that has them in wet  
15 work a lot. Otherwise, it's all e. coli, and you know  
16 where that came from.

17 MR. GUZEWICH: Yes. I'll point out to you  
18 that, although we have a difficult time getting  
19 compliance with hand washing in this country, at least  
20 a lot of people here know that's an expectation. We  
21 do have people working in this industry who come from  
22 places where that's not an expectation.

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1 CHAIRMAN BRASS: Yes, Dr. Neill?

2 DR. NEILL: Having taken my daily dose of  
3 Triclosan this morning in the form of toothpaste,  
4 which is now on the market, I'm pleased that somebody  
5 is interested in determining the extent to which the  
6 entry of these types of materials into the food chain  
7 is going to affect my health or that of my children or  
8 those of my patients.

9 That aside, this whole food handling issue  
10 seems prone -- engenders an important question for me,  
11 which I'm not sure I heard an answer to.

12 One is the testing that has been proposed  
13 as a surrogate to clinical trials for non-food  
14 handlers does not have, it would seem, except in the  
15 epidemiologic data and the case data that the various  
16 public health departments generate -- doesn't seem to  
17 have an equivalent, and I'm looking for an answer to  
18 you as to whether you feel the proposed surrogate  
19 tests in the monograph from '94 in any of their forms  
20 are reasonable to use in the food handling preparation  
21 category.

22 MR. GUZEWICH: I don't know the answer to

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1 that, because it hasn't been tested that way. That's  
2 the whole problem. We rely on epidemiologic  
3 information. There has been a certain amount of --  
4 There have been a few studies of hand worker -- food  
5 worker hands. Okay, there hasn't been none. But  
6 there's relatively few -- a small body of science in  
7 that area.

8 So the question that we are struggling  
9 with is how much of that information from the clinical  
10 experience and setting can be translated, and we don't  
11 have a good way to analyze that. Anything this panel  
12 can say in that regard would be very helpful to us,  
13 because we don't know what to make of it.

14 We're very much embroiled in this issue of  
15 food worker hands, and should they be prohibited from  
16 bare hand contact or is hand washing acceptable or is  
17 hand sanitizer acceptable or some combination of that?

18 We have some very strongly held opinions  
19 on all sides of that. The industry doesn't always  
20 agree with us on this issue. The food service  
21 industry, I'm talking about now, and the retail food  
22 industry.

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1           We're looking for the science to base our  
2 decisions on, and the earlier speaker was here on  
3 microbial modeling. The FDA under the Food Safety  
4 Initiative, one of our major thrusts is to get more  
5 into the area of microbiologic modeling of food borne  
6 disease and to look at that in terms of maybe coming  
7 to the decision making process and the whole risk  
8 analysis system.

9           So we're looking to go toward that way and  
10 to have the scientific data upon which to make models.  
11 Our problem right now is there's so little data that  
12 you can't even begin to design your models, and our  
13 scientists are scratching their heads, desperate.

14           We're going to be paying people all kinds  
15 of bizarre things to get some basic data so we can  
16 develop models. So I don't have a good answer,  
17 because we're asking the same questions.

18           CHAIRMAN BRASS: Dr. Maki?

19           DR. MAKI: I would just say again, I think  
20 the evidence in the health care setting, and  
21 particularly the greatest challenge for preventing  
22 spread of organisms that are transmitted on hands, is

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1 in the hospital critical intensive care unit..

2 There, barriers -- Pretty good data  
3 indicate the use of barriers where people don't touch  
4 with bare hands significantly reduces transmission.  
5 There's data, certainly, in epidemics. There's  
6 endemic data that suggests that is beneficial.

7 I, frankly, think that trying to improve  
8 compliance in an industry where people are already '  
9 stressed to the max and they're going to continue to  
10 work when they're ill, I don't care what you say --  
11 it's going to be hard to get them to wash their hands  
12 more than ten or 15 seconds, if they wash them  
13 frequently enough.

14 I think finding a way effective to use  
15 barriers, whether they use instruments or they use  
16 gloves -- I don't think food workers should touch or  
17 handle any food that's not going to be cooked well  
18 after they handle it.

19 MR. GUZEWICH: You're right where I am on  
20 that subject, and barriers is the word we use; but I  
21 also would like to suggest that you would agree, I'm  
22 sure, that we still would like surgeons to wash their

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1 hands before they put the gloves on; and we feel the  
2 same way about food workers. They should still be  
3 washing their hands even if they do go to the barrier  
4 method.

5 DR. MAKI: The use of barriers is not a  
6 means to discourage hygienic hand washing where it  
7 should be done.

8 MR. GUZEWICH: To pick up on that phrase,  
9 I mean it's multiple barriers. Ideally, they  
10 shouldn't be coming to work if they're ill, and then  
11 they would not -- then they would be washing their  
12 hands as well, and they would have the barrier. We  
13 would have three barriers in place.

14 Our problem now is that we can't get  
15 compliance on any of those barriers.

16 DR. LARSON: Well, I'm just not convinced  
17 that there's any evidence that 20 seconds is a magic  
18 number, any better than 15 or maybe even ten. The  
19 problem, when we make rules that are sort of -- the  
20 attitude is, well, if ten is good, 20 is probably  
21 twice as good. That's not true. We all know that.

22 So people -- The unrealistic rules make

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1 compliance even more impossible, because if you count  
2 20 seconds, it is forever, and it just is almost like  
3 if we under-rule rather than over-rule, we'll have  
4 perhaps less problem with compliance, because people  
5 then blanket say, well, this is not doable.

6 MR. GUZEWICH: Your point is well taken,  
7 and like I told you before, I do not know specifically  
8 where they got that number 20 seconds. I will try to  
9 find that out and get back to you on that, but if this  
10 group could give us advice in that area and feel that  
11 some other duration would be better, we're open to all  
12 kinds of input. We always want input on these kind of  
13 things. We really do.

14 DR. LARSON: Yeah. There are good data  
15 from Wenzell that do show that ten seconds is probably  
16 equivalent to 15 at least. I don't know about 20.

17 CHAIRMAN BRASS: Thank you. It's now  
18 Noon. I know this has made me hungry. It's  
19 lunchtime.

20 I'd like to reconvene promptly at one for  
21 the public session, because we have scheduled peoples.

22 Thank you very much.

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1 (Whereupon, the foregoing matter went off  
2 the record at 12:03 P.M.)

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## A F T E R N O O N   S E S S I O N

Time: 1:02 p.m.

CHAIRMAN BRASS: If we can start to reconvene, please.

Our next series of speakers will be those who have requested time in the open public hearing. As I introduce each of the individuals who will be speaking, I would request that each of them identify not only their current affiliation but any sponsorship for their activities today and any conflicts of interest that they feel appropriate to disclose to the panel.

Our first speaker will be Dr. Abdul Zafar.

DR. ZAFAR: My name is Abdul Zafar. I work in the Arlington Hospital, which is 15 miles from here, and is a 450 bed acute care teaching hospital, and I there for the last ten years managing the infection control department.

I am here to present our findings of a study of the request of industry. This is the hospital I'm talking about.

We had this outbreak of MRSA, methicillin

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1 resistant staph aureus. We don't expect these  
2 infections in the nursery, and so when we saw the  
3 first case, we had great kind concern.

4 This is the whole outbreak. We never saw  
5 that infection in the nursery, as I told you, but it  
6 was there. We see infections in generally 1990.  
7 There's the first or index case. Then we see all  
8 these infections.

9 Because of the severity of the infection,  
10 literally I moved my office to the nursery, and we did  
11 many things to control that outbreak. All the  
12 infections were in the male infants. So we are  
13 looking at what different things we are doing for the  
14 male infants, and these are the different methods we  
15 took in the month of February.

16 Everything is still exploratory. Even  
17 then we kept on seeing this outbreak. Then in April  
18 we made a change in our hand washing policy and the  
19 infant bathing policy. The changes: To institute  
20 Triclosan 20 percent for infant bathing and hand  
21 washing.

22 Although we did not have an -- of use of

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1 2.3 percent Triclosan in the infant, but we had to  
2 take the chance, and soon after that change you can  
3 see the change.

4 Since then, there has been no MRSA  
5 infection in our nursery.

6 CHAIRMAN BRASS: Does that complete your  
7 comment?

8 DR. ZAFAR: Yes.

9 CHAIRMAN BRASS: Are there questions or  
10 comments from the panel? Thank you.

11 Our next speaker is Paul Marshall, and  
12 again if you could identify your current affiliation,  
13 any sponsorships or conflicts of interest, please.

14 DR. MARSHALL: Good afternoon, ladies and  
15 gentlemen. Thank you for the opportunity to come here  
16 to present the results of some findings that we did on  
17 research on reducing MRSI using Triclosan.

18 The first thing I'd like to state is that,  
19 although I am here sponsored by the trade, the  
20 interesting thing with this research was that the  
21 companies whose products were used in it didn't know  
22 what was going on, and I had the absolute fabulous

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1 pleasure of watching the national sales manager for  
2 both Johnson & Johnson and Reckett & Colman have their  
3 mouths drop wide open when I presented the paper.

4 Why is somebody from the Antipodes is up  
5 here talking to you, august body over here in the  
6 states? I am an infection control consultant. I have  
7 been for the last eight years, and prior to that I was  
8 actually working at St. Vincent's Hospital in Sydney ,  
9 where I ran the MRSA isolation unit.

10 That ward was probably the most difficult  
11 challenge that anybody could look after, because we  
12 used to look after any patient with MRSA, whether they  
13 were a heart/lung transplant, heart transplant, burns,  
14 bone marrow transplant, you name it. Whatever came  
15 across the door and got infected, we got.

16 It really got me quite interested in  
17 seeing what was going on with MRSA and ways that we  
18 could actually reduce it. Currently, I'm working at  
19 this gorgeous little hospital called the Sutherland  
20 Center for Nursing and Medical Excellence. It's  
21 situated on the southern extremity of Sydney and right  
22 in the middle there is the actual city of Sydney.

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1 It's about 25k out of the city itself.

2 All of us are worried about infections in  
3 hospital, and the way that those infections impact on  
4 our patients, and that's the basis for any clinical  
5 investigation, is what happens to the patients  
6 themselves.

7 Bugs are sneaky little things. You can  
8 have one sitting there, anywhere. Any opportunity for  
9 it to get in, and it will take hold, then operate like  
10 rabbits. And what do we get at the end of it?  
11 Anything. It can be a cellulitis for a patient.

12 Infection can actually cause damage itself  
13 and cause ulcers or it can infect iatrogenic problems  
14 such as pressure areas. This is my pressure area,  
15 because all of them are connected.

16 It can also affect very, very unusual  
17 conditions. This is a patient with an unusual  
18 manifestation of mycoses fungoides, and with mycoses  
19 any irritation on the skin itself will end up with  
20 another lesion coming through. So treating this  
21 patient, who is heavily colonized and infected,  
22 actually, with MRSA and pseudomonas, we had to be able

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1 to try and find something that was very, very low  
2 irritant to treat him.

3 It also affected his legs, and the one on  
4 the righthand side -- that channel actually went right  
5 through to the other side of his foot.

6 It causes surgical problems. Infected  
7 amputations can take forever to heal because of the  
8 impaired vascularity. Patients can have small  
9 pressure areas which actually get infected. In the  
10 case of this patient, we actually asked the plastic  
11 surgeons just to clear it up a little bit for us, and  
12 they just kept on cutting and cutting and cutting and  
13 cutting.

14 This patient, by the way, had no elevated  
15 white cells, no increasing neutrophil percentage, no  
16 temperature whatsoever, but that was the condition of  
17 his foot.

18 It can cause problems such as necrotizing  
19 fascitis, in this patient who came in for just an open  
20 and close laparotomy of CI of the stomach. It can  
21 cause beautiful problems when you've got any  
22 vasculature artificial graft done, such as in this

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1 patient with a fem fem crossover graft; or in a worse  
2 case scenario, this patient who, unfortunately, had a  
3 fem fem crossover graft performed which got very, very  
4 heavily infected with MRSA, infarcted one leg, and we  
5 actually had to slice through the leg to try and save  
6 her life.

7 All of those patients had MRSA. None of  
8 them died from MRSA. If they died, it was due to  
9 their underlying problems, not infection. That is one  
10 hell of an achievement for any hospital to state, that  
11 we were able to control and contain infection to the  
12 point where it did not cause mortality. May have  
13 contributed to a morbidity, but definitely not  
14 mortality.

15 The problem is with MRSA in other patients  
16 or other organisms is what are you dealing with. You  
17 only know if you swab someone. The only way you can -  
18 - most hospitals look after MRSA is trying to identify  
19 patients with a positive isolate from routine swabbing  
20 and institute some sort of treatment for those, but  
21 that's not really good enough; because what about  
22 those that you don't know about.

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1           We did investigations to find out roughly  
2           how long it was from the time a patient was instituted  
3           -- admitted to the institution -- that's better -- to  
4           actually showing the first signs of MRSA and  
5           colonization swabbing, and it was 13.4 days.

6           So we're saying that that patient had a  
7           hospital acquired MRSA, because it was 13.4 days after  
8           they came in or just we didn't swab that one ,  
9           particular place? The only way you can find out,  
10          really, if all of your patients do have multi-  
11          resistant organisms is if I got everyone of you, if  
12          you were patients of mine, stuck you in a vat of  
13          media, ask you to breathe three times and pass flatus.  
14          Then I could effectively say you did not have MRSA  
15          carriage.

16          To try and treat everybody -- why not  
17          treat everybody? Treat the pool. That way you get  
18          rid of cross-infection. So that's what we wanted to  
19          do, to try and work out a way that we could treat all  
20          patients in the hospital to reduce the potentiality  
21          for getting MRSA, but there are many, many factors  
22          come into play with MRSA, and things that can change

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1 what you're looking for.

2 Were there alterations in the skin  
3 preparation used in the theaters? Were there changes  
4 in hand washing solutions or hand care solutions?  
5 Were the cleaning products going to be changed? Did  
6 the cleaning protocols have anything to do with the  
7 patients itself? What about antibiotic usage? Were  
8 they consistent? Did they change?

9 We tried to work out a way that we could  
10 look at one variable and one variable alone, and that  
11 was introducing Triclosan body washing.

12 We brought that in in the form of  
13 Microshield T as a body wash solution for all  
14 patients, if they were bedfast. They were given their  
15 own supply and now washed with that or booked  
16 admissions for surgery were asked to buy Sapoderm  
17 soap, to have two preoperative washes before they  
18 came in, and then used the Sapoderm soap or the wall  
19 mounted Triclosan solution that was instituted in all  
20 the bathrooms in the hospital.

21 They are asked to do that, and we checked  
22 on them to see what was going on. I'm very sneaky.

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1 You tell nurses what to do. Then you go and ask the  
2 patients if they're doing it, and that's what I ended  
3 up doing, going around and doing spot checks on the  
4 patients to see if the nurses were actually complying  
5 with what we're asking them to do.

6 It was only a small exercise, because we  
7 did it over six months. In the control period, which  
8 was the six months in the year before to get rid of  
9 any seasonal variation, there was 11,500 patients that  
10 we used as a control, and in the trial there were  
11 12,860.

12 These were patients that were not -- that  
13 were in hospital for over 24 hours. So any daily  
14 patients were excluded.

15 We looked at the development of any new  
16 hospital acquired or community acquired isolates of  
17 MRSA. We looked at their antibody sensitivities. We  
18 actually looked at the phage type and the site where  
19 the MRSA was first detected.

20 The results of that were new hospital acquired  
21 MRSA in the period reduced statistically to a p value  
22 of .00176. For the first time, we were able to show

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1 that the introduction of one variable or the  
2 alteration of one variable in the form of Triclosan  
3 body washing was able to significantly reduce MRSA  
4 carriage and infection within the hospital itself.

5 When we looked at the sites, although they  
6 weren't statistically significant, they are  
7 interesting to note, because the wound swab results  
8 dropped, and the nasal carriage dropped as well, which  
9 is what you would anticipate with MRSA actually being  
10 shed a lot through the hospital on skin flakes as well  
11 as on staff hands and on the ties that all of us are  
12 wearing at the moment.

13 What we found that was quite interesting,  
14 and here my computer went berserk, is the  
15 ciprofloxacin sensitivity. Before -- The six months  
16 before we started the Triclosan, 8.3 percent of all  
17 our MRSA isolates were actually sensitive to  
18 ciprofloxacin, and that paralleled with the Australian  
19 Group on Antibiotic Resistance, the AGAR group, that  
20 says between five and ten percent of all MRSAs in  
21 Australia are sensitive to cipro.

22 During the trial that increased to 17.4

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1 percent. After the trial we continued using the  
2 Triclosan because it was so effective. It went up to  
3 22.5 percent for the six months following.

4 We were able to show that, looking at new  
5 isolates, we reduced the MRSA that came through. We  
6 found that there was a change in the antibiotic  
7 sensitivities for the MRSA. We detected changes in  
8 the phage typing that came through as well,  
9 particularly in the reduction of one particular phage,  
10 which was -- I'll check my notes -- a phage that  
11 contained 85/95.

12 The first site detected, we also found a  
13 decrease in wound swabs and in, as I said, nasal  
14 carriage.

15 Where do we go from this further? We have  
16 to look at ways that we can see if our findings,  
17 particularly in relation to phages and the  
18 ciprofloxacin sensitivity, are being able to be proved  
19 directly from the use of the Triclosan, but I think  
20 we've been able to find, and I'm taking some of the  
21 comments that were made earlier -- we tried to find,  
22 by using one variable change over a significant number

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1 of patients, that the variable such as a topical  
2 antimicrobial wash could effectively reduce the  
3 carriage of MRSA within our hospital.

4 With the evolution of multi-resistant  
5 organisms throughout the world, the judicious use of  
6 topical antimicrobial agents is something we as a  
7 scientific body should look at.

8 Thank you kindly.

9 CHAIRMAN BRASS: Thank you. Are there any  
10 questions from the panel? Yes, Dr. Larson?

11 DR. LARSON: We've done a couple of  
12 studies like this, and as I mentioned before, always  
13 a big confounder has been when there's been a change  
14 in infection rates on certain units and hand washing  
15 frequency changes.

16 Do you have any -- Did I miss that? Did  
17 you talk about the frequency of hand washing?

18 DR. MARSHALL: Yes. With the hand washing  
19 solutions, it was like walking around with my mouth  
20 taped over, chomping at the bit; because people were  
21 allowed to do what they had been doing, and my job was  
22 to see that there were no changes.

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1           So I couldn't go around and say your hand  
2           washing technique is lousy, let's fix it up. I had to  
3           just bite my tongue, because that person has been  
4           doing it for the last two years, and I'm not going to  
5           change that.

6           I wanted very, very much so to make one  
7           variable only.

8           DR. LARSON: No, but my question is: '  
9           During the time of the change, did you have any --  
10          I'll give you an example. In the middle of a similar  
11          trial we had a VRE outbreak, and we had to tell people  
12          to wash their hands more.

13          So here we are testing a product at the  
14          same time as the frequency of hand washing tripled.

15          DR. MARSHALL: Right. If I was in that  
16          situation -- we luckily, so far, haven't had any VRE  
17          in the hospital. If that occurred, I would have to  
18          terminate it, because that's not a variable, and my  
19          aim was to change one variable alone, and I would have  
20          had to shorten the period of the trial because of that  
21          event.

22          CHAIRMAN BRASS: Other comments? Thank

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1 you.

2 The final speaker in the open public  
3 hearing is Dr. Syed Sattar.

4 DR. SATTAR: Good afternoon. Thank you  
5 very much for giving me this chance to express my  
6 views on the importance of viruses and their  
7 elimination from hands. Some other speakers have, in  
8 fact, set the stage for me very nicely, making my job ,  
9 somewhat easier in this regard.

10 I am a professor of microbiology, and I am  
11 also Director of a recently created Center for  
12 Research and Environmental Microbiology at the Faculty  
13 of Medicine, University of Ottawa in Canada.

14 I would like to give you a very quick  
15 overview of what I am to present here, give you my  
16 perspective of the situation with regards to  
17 infectious diseases in the United States, talk to you  
18 a little bit about where viruses fit as disease agents  
19 in this picture, talk about the role of hands in the  
20 spread of viral infections, show you some data from  
21 our studies accumulated over several years about how  
22 well certain types of viruses survive on human hands,

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1 and what implications it has in terms of those  
2 surviving viruses to be transferred from hands to --  
3 from contaminated hands to clean hands or from  
4 contaminated hands to clean surfaces that those hands  
5 touch, and then show you some data on the use of hand  
6 wash/hand rub products and their potential to  
7 eliminate viruses from such contaminated hands, and  
8 then conclude a few remarks at the very end. Thank '  
9 you.

10 I'd like to point out that I have been  
11 conducting research on infection control with  
12 particular emphasis on chemical germicides for many  
13 years now, and the Center was set up with this  
14 research focus in mind. Because of this, I have  
15 conducted studies sponsored by many of the companies  
16 present here, because over the years we have been  
17 given contracts to conduct research.

18 My visit here is also being sponsored by  
19 the industry coalition.

20 My concern has been, and I have made this  
21 remark wherever I have had an occasion to, is to say  
22 that the tentative final monograph totally ignores

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1 viruses.

2 When I raised that question two years ago  
3 in an FDA meeting discussing the health care continuum  
4 model, I was told that the FDA may consider issuing a  
5 separate monograph dealing with viruses; and if that  
6 exercise is going to be as slow as the one that we are  
7 dealing with now, then I certainly won't be around to  
8 see it materialize.

9 So I think it's an issue that we need to  
10 come to grips with, and I think the data that Dr.  
11 Guzewich presented reinforces the point that I am  
12 going to be making here, or I will reinforce the point  
13 that he has made. The next one, please.

14 With regards to infectious diseases in the  
15 United States, the picture is in fact changing, and in  
16 some ways not for the better. These are data from the  
17 CDC, a publication by Pinner et al. in 1996, which  
18 shows that between 1980 and 1992 there has actually  
19 been a 58 percent increase in fatalities due to  
20 infectious diseases; and if you take away the  
21 contribution of HIV as the infectious agent, that  
22 increase still amounts to about 22 percent.

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1           Those are, I believe, sobering numbers.  
2       As a result of this increase, infectious diseases now  
3       rank as the third leading cause of death in the United  
4       States. There are -- These are rough estimates, I  
5       would imagine, suggest that more than 166,000  
6       fatalities due to infectious diseases, and that, of  
7       course, amounts to more than eight percent of the  
8       fatalities recorded in the United States in any given  
9       year in recent years.

10           In addition to fatalities, infectious  
11       agents also cause more than 740 million clinical cases  
12       of disease per year, and such infections account for  
13       25 percent of all visits to physicians, and a very  
14       crude estimate is that this has an impact on the  
15       economy of the United States in terms of \$120 billion  
16       per year.

17           Now these figures do not take into account  
18       the impact due to delayed outcomes such as post-polio  
19       syndrome and so on, and synergistic effect. There is  
20       now some evidence to suggest that relatively mild  
21       infectious agents, if they are affecting individuals  
22       who have been pre-exposed to certain kinds of

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1 industrial chemical, might in fact suffer much more  
2 serious side effects than any one of these two  
3 components on its own.

4 Then we don't have any data, any credible  
5 data, on the productivity years of life lost. Thank  
6 you. Next one.

7 What are the viruses that I want to talk  
8 to you about? Here is a list. I think it's a pretty ,  
9 complete list of viruses that have a strong potential  
10 to spread through contaminated hands: Hepatitis A  
11 virus, which causes infectious hepatitis, and it is  
12 frequently involved in food borne outbreaks and also  
13 outbreaks in childcare centers; rotaviruses, among the  
14 major causes of acute gastroenteritis throughout the  
15 world and, certainly, United States is no exception.

16 Every year in the cool and dry period of  
17 the year, you see outbreaks of rotaviral  
18 gastroenteritis in institutional settings, nursing  
19 homes, daycare centers, hospitals, and schools as  
20 well.

21 Chylisi viruses are a somewhat more  
22 amorphous group, but among Chylisi viruses the Norwalk

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1 agent certainly is an important cause of acute  
2 gastroenteritis, and this spreads in institutional  
3 settings as well as related to food borne spread.

4 Rhinoviruses, which are the major cause of  
5 the common cold, now only survive well on human hands,  
6 which I will show you some data for, but they also  
7 have been shown to spread through contaminated hands.  
8 These studies were done -- quite elegant studies -- by  
9 Dr. Jack Watney over the past several years to  
10 substantiate this particular relationship between  
11 contaminated hands and the spread of the common cold  
12 caused by rhinoviruses.

13 Adenoviruses cause eye infections,  
14 gastroenteritis and other types of infections, and  
15 these are quite a problem in eye clinics where the  
16 hands of ophthalmologists have been incriminated as  
17 the vehicle for the spread of adenoviruses.

18 Enteroviruses are an even more amorphous  
19 group, but they causes infections such as hemorrhagic  
20 conjunctivitis, gastric infection, central nervous  
21 system infections, and a variety of other clinical  
22 conditions in humans. Next one, please.

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1           As I said, this histogram consists of data  
2           that we have generated over many years, and as you can  
3           see, rotavirus after its placement on the hands of  
4           adult volunteers and when they were sampled 20 minutes  
5           after that inoculation, you could detect nearly 60  
6           percent of the infectious virus still being alive.

7           Similarly figures for rhinoviruses, and  
8           these compare extremely well with staphylococcus .  
9           aureus, which is a virus which is by nature designed  
10          to live on human skin. It eventually dies, of course,  
11          depending on the type of strain that you're talking  
12          about, but the one that survives the best in our hands  
13          has been hepatitis A virus.

14          We have shown that even after four hours  
15          of such sampling nearly seven percent of the virus  
16          still remains viable, and that is, of course, half a  
17          normal person's work day. If they don't wash hands  
18          during that period, then they could carry substantial  
19          amounts of hepatitis A virus on their hands.

20          In contrast to this, enveloped viruses --  
21          these are all nonenveloped viruses that I'm talking  
22          about. Enveloped viruses such as parainfluenza virus

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1 do not do well on human hands, and there is no  
2 evidence that they actually spread through  
3 contaminated hands.

4 So there seems to be some direct evidence  
5 or indirect evidence to suggest that those viruses  
6 that do better on human hands have a stronger  
7 potential to be spread through such contaminated  
8 hands.

9 E. coli, a bacterium, a gram negative  
10 bacterium, doesn't do well, and this is also mentioned  
11 by Dr. Leyden a few minutes ago. Next one, please.

12 We have conducted some studies to show  
13 what happens when hands interact with other hands and  
14 when they interact with environmental surfaces in  
15 everyday settings. We have been able to do this  
16 through three models.

17 We had contaminated hands touching clean  
18 metal disks. We had metal disks which were clean,  
19 which were contaminated touching clean hands, and then  
20 one contaminated hand touching a clean hand, just to  
21 try and quantitate how much infectious virus can be  
22 transferred.

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1 In this case, we worked with a rotavirus  
2 which was actually suspended in a ten percent fecal  
3 suspension to simulate as closely as possible a  
4 natural situation.

5 As you can see, if the inoculum was  
6 allowed to dry for 20 minutes, there was 16 percent to  
7 about eight percent transfer, depending on which model  
8 you were talking about. This was a ten second contact  
9 with a very light pressure, which is only about one  
10 kilogram per centimeter square, which is not an  
11 unusually high pressure. This is the pressure that  
12 you encounter in many, many everyday situations.

13 I would also like to point out that these  
14 experiments were done without any friction during this  
15 contact. If you apply friction along with this  
16 contact, then you can actually increase the level of  
17 transfer by two to threefold. So friction plus  
18 contact, even more important in terms of virus  
19 transfer.

20 Next one, please. In terms of  
21 interrupting the spread of viral infections in  
22 whatever setting that you may want to consider, I'd

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1 like to present to you this general scenario.

2 You have a virus being released, either in  
3 feces or nasal secretions or ocular secretions. If  
4 that released virus contaminate hands and if that  
5 virus then manages to survive on those hands, you can  
6 have direct inoculation of that individual or another  
7 individual in the care of this person going directly  
8 from those contaminated hands.

9 Hands can also transfer that virus over to  
10 other vehicles, and that other vehicle can eventually  
11 also lead to exposure of susceptible individuals in  
12 that particular setting. This may result in  
13 infection, and cases of infection may result in  
14 disease. Not all cases of infection result in a  
15 clinical case of disease.

16 Whether it is an infection or disease,  
17 there is shedding of virus from that infected case.  
18 So you have that cycle repeating itself again.

19 If you want to interrupt this, one of the  
20 means in terms of the use of germicides is that you  
21 bring that germicide in either through decontamination  
22 of hands or decontamination of environmental surfaces,

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1 and you can, in fact, interrupt that transmission.

2 I will show you some data from our own  
3 work. Next one, please.

4 If you look at the case of two viruses  
5 that, again, we worked with, hepatitis A virus and  
6 polio virus, if you wash experimentally contaminated  
7 hands with 70 percent ethanol, there was such a high  
8 level of reduction in the level of both of these  
9 viruses that one could not show any transfer from such  
10 hands to environmental surfaces.

11 On the other hand, if we used an  
12 antibacterial soap with .3 percent Triclosan, there  
13 was .6 percent transfer in both of these cases.  
14 Unmitigated soap, on the other hand, gave you somewhat  
15 higher transfer, and tap water alone with about .5  
16 parts per million free chlorine gave you between 3 and  
17 4 percent transfer.

18 Next one, please. If you like to look at  
19 the relative efficacy of hand wash agents in reducing  
20 the contamination, this set of experiments is based on  
21 our work with rotaviruses. If you take 70 percent  
22 isopropanol or 70 percent ethanol, they are extremely

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1 good in their rotavirus inactivating activity, and  
2 more than 99 percent of these viruses could be  
3 eliminated within a contact time of about ten seconds,  
4 which I believe is much more realistic than 20  
5 seconds.

6 On the other hand, if you take unmitigated  
7 liquid soap, the level of reduction was approximately  
8 76 percent, which in fact wasn't much better compared  
9 to tap water. Next one, please.

10 This is a more recent study that is still  
11 under progress. This is why I'm not giving you  
12 standard deviations and so on, because we haven't  
13 really analyzed the data. I just want you to focus on  
14 the trends here.

15 We have tested an antiseptic gel which  
16 contains 60 percent ethanol. There is close to a 3  
17 log reduction in the amount of infectious rhinovirus  
18 on the hands of these adult volunteers.

19 If you take a hand sanitizer which has a  
20 62 percent ethanol, the level of reduction is, in  
21 fact, 4 logs or greater. Then if you take a hand  
22 rinse which has 78 percent ethanol plus chlorhexidine

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1 gluconate, the level of reduction was just over 2  
2 logs.

3 With standard hard water containing 200  
4 parts per million of calcium carbonate, the reduction  
5 was about 90 percent. The question is: Is this  
6 significant between hard water rinse and these other  
7 products?

8 I'd like to submit that, yes, it is  
9 significant, because this is a tenfold difference. if  
10 you were to do statistical analysis, you probably  
11 would find that there is significance.

12 The other factor that I'd like to  
13 emphasize here is that most of these viruses, and this  
14 was again alluded to by John Guzewich earlier on, have  
15 a very small minimal infective dose. So the higher  
16 the level of reduction that you can achieve, the  
17 higher is the level of risk reduction and risk  
18 management. Next one, please.

19 This, in fact, should say concluding  
20 remarks here. Viruses are important pathogens, and  
21 one cannot deny that, especially in daycare centers,  
22 hospitals, food handling establishments, and also in

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1 nursing homes.

2 Many viruses can survive well on human  
3 hands. Therefore, human hands can have the potential  
4 of being able to access vehicles for such viruses.  
5 Many viral infections can be indeed spread through  
6 contaminated hands, and hand washing or use of hand  
7 rub agents have been shown to be effective against  
8 several types of viruses, but we need to do more  
9 studies in the particular context.

10 Such effective agents can also interrupt  
11 the transfer of viruses, therefore can interrupt the  
12 chain of spread of viral infections. I believe, and  
13 I am willing to discuss this point even further, is  
14 that in situ virus inactivation is not necessary.

15 With alcoholic rubs, there is in situ  
16 inactivation, because there is no subsequent washing  
17 of hands; but if there is a product such as a soap  
18 which dislodges your viral contamination and you can  
19 wash it off with subsequent rinsing in water and  
20 drying or whatever, I believe that the end result is  
21 achieved.

22 So one must not really insist on in situ

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1       inactivation. If you were to do that, you would  
2       require much more potent products which, I can  
3       guaranty you, would not be user friendly. Therefore,  
4       you would, in fact, create a problem of reduced  
5       acceptance and compliance.

6               Testing of surgical scrubs, preoperative  
7       skin preps and body washes is not necessary against  
8       viruses, simply because viruses are not found as a  
9       part of the resident flora of human skin. Therefore,  
10      the emphasis has to be on hands, hand washing or hand  
11      decontamination agents.

12             I believe that, if you use the right  
13      products with the right degree of compliance, you  
14      will, in fact, lead to a reduce risk of spread of  
15      infection in daycare centers, in food handling  
16      establishments, in nursing homes, and in many hospital  
17      situations.

18             Thank you, very much.

19             CHAIRMAN BRASS: Thank you. Comments for  
20      Dr. Sattar from the panel? Thank you very much.

21             DR. LARSON: Actually, could I just --  
22      Sorry. In your next to last slide you talk about an

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1 antiseptic gel, a hand sanitizer, and a hand rinse.

2 If I were a consumer or a food handler, I  
3 would think those are extremely different products.

4 DR. SATTAR: Yes.

5 DR. LARSON: And you know, I'm not sure  
6 they are. Could you say why you use those terms?

7 DR. SATTAR: Yes. Indeed, I am using the  
8 terms that were provided to us by the sponsor, and I  
9 am also not privy to the entire formulation.

10 The active ingredients were listed as  
11 being either alcohol alone or alcohol and  
12 chlorhexidine gluconate, and I believe that the intent  
13 of the sponsor is that they are meant for different  
14 uses and different settings.

15 CHAIRMAN BRASS: As we heard today, this  
16 discussion has been going on for 25 years. Therefore,  
17 this esteemed panel should have no trouble in  
18 resolving the issues over the next two hours. That's  
19 why they gave us two instead of one.

20 Perhaps to get us started in our  
21 discussion, if I could ask Ms. Lumpkins from the FDA  
22 to give us some focus and orientation as to our

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1 objectives.

2 MS. LUMPKINS: You give me the hard part.

3 Seems to me that the discussion has been  
4 sort of coming from all over everywhere, and the only  
5 way that I can see to focus it is to try and go back  
6 to the performance attributes that I discussed earlier  
7 today and see if we can come to -- well, not even any  
8 conclusions, but if we can discuss in the context of  
9 broad spectrum, persistence, fast acting, what the  
10 committee feels might be appropriate for a  
11 demonstration of each one of these traits.

12 Let's try and stay away from, if we can,  
13 particular products or technical discussions on the  
14 merits of different types of testings, and just in  
15 very general terms.

16 Then the second question is whether or not  
17 these particular attributes have got to be specific  
18 for each drug product category. So the same  
19 discussion points.

20 That makes sense to me -- I'm not sure  
21 that Dr. Katz agrees -- to start with should they be  
22 specific for each product use, and go from there;

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1 because it may make a difference on your discussion of  
2 broad spectrum.

3 In other words, if you decide that one  
4 test fits all, it makes a difference to, well, broad  
5 spectrum. Do we tailor it to the use of the product  
6 or do we not?

7 CHAIRMAN BRASS: So would you like a  
8 discussion of the attributes or the testing first?

9 MS. LUMPKINS: Basically, for each  
10 attribute what do you consider an appropriate  
11 demonstration that a product has over a spectrum, but  
12 I think probably the better way to approach it is to  
13 say should this be product -- intended use specific?

14 In other words, would the spectrum that we  
15 would like to see for a patient prep or skin prep  
16 necessarily be the same we want to see for food  
17 handlers? I suspect that the answer is going to be  
18 no, which is why I thought maybe we might want to get  
19 that question out of the way first.

20 CHAIRMAN BRASS: Okay. Why don't we  
21 address that question specifically first then. That  
22 has to do with the broad categories of products as

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1 defined in the monograph, as well as the general  
2 question that's listed as point 2, should testing  
3 requirements be based on intended use and, if so, how.

4 MS. LUMPKINS: Right, and don't focus in  
5 on what particular types of products. If there's any  
6 way that you can group them, let you see that there  
7 might be some similarities as suggested by some of the  
8 speakers today, then that's fine.

9 CHAIRMAN BRASS: Okay. We'll try starting  
10 there. What I'd like to do as a format is go around  
11 the table and ask each member of the panel if they  
12 have anything to contribute, to make some comments.

13 If someone from the panel, industry or any  
14 of our consultants have a response or an elaboration  
15 based on the specific comment made, please feel free  
16 to do so.

17 I would ask those people who are not on  
18 the panel to simply move to a microphone. I will try  
19 to recognize you. If I don't, wave your hand and, if  
20 that fails, then and only then feel free to throw  
21 something at me, but don't hit Dr. Koda-Kimble.

22 Okay. So perhaps, Dr. Larson, you would

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1 like to get us started on the issue of different  
2 indications or different intended uses of these  
3 products and its impact on the monograph and testing.

4 DR. LARSON: Actually, I was just hanging  
5 out here, because the table is comfortable. I'm not  
6 really on the panel.

7 CHAIRMAN BRASS: You moved back.

8 DR. LARSON: Thanks for the invitation.

9 CHAIRMAN BRASS: No, your name is on my  
10 list. So you are --

11 DR. LARSON: Well, it seems to me that if  
12 something is broad spectrum, it's broad spectrum. I  
13 mean, those two questions aren't mutually exclusive.

14 Yes, we probably will want different  
15 agents for different uses, but I think those  
16 characteristics have been defined, and there's not a  
17 lot of need to spend a lot of time defining what broad  
18 spectrum is.

19 CHAIRMAN BRASS: What about the  
20 differences in issues like persistence, onset?

21 DR. LARSON: Well, again, either an agent  
22 has persistence or it doesn't. The question is when

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1 do we need it? The issue is not what are -- if, in  
2 fact, -- I mean, I think those things have been  
3 defined. What hasn't been defined is do we -- as Dr.  
4 Maki suggested for surgical applications and pre-op  
5 skin preps, persistence would be, I would think, at  
6 least theoretically and based on clinical evidence  
7 that he and others have shown, a good characteristic.

8 I made the suggestion that there doesn't  
9 seem to be any clinical evidence that I know of -- and  
10 I may be wrong; please jump up and correct me -- for  
11 a value added for persistence for a health care  
12 personnel hand wash.

13 So maybe those are the kinds of issues to  
14 discuss.

15 CHAIRMAN BRASS: In some of your comments  
16 and others, you mentioned the appropriateness on an  
17 intended use base differentiation between resident and  
18 transient organisms. Would you like to add anything  
19 to your earlier comments?

20 DR. LARSON: Not really. I do think it  
21 would be a useful discussion to talk about whether the  
22 -- we keep -- Seems to me that these food worker --

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1 the food handling requirements, etcetera, are  
2 different not for any rational basis, but because they  
3 were regulated under a different group before, and  
4 they've just come into a new -- and so basically, what  
5 we're doing is we're taking two groups and putting  
6 them together, and artificially --

7 There are some differences in need there,  
8 but maybe not as many as we might think initially. .  
9 You either need an antiseptic or not, and if you need  
10 one, do you need persistence or not? That's the  
11 question, I think.

12 CHAIRMAN BRASS: Okay. Which you implied  
13 in general framework of answer. Thank you.

14 Dr. Rice?

15 DR. RICE: I would tend to concur with Dr.  
16 Larson's comments. I don't have anything additional  
17 to add.

18 CHAIRMAN BRASS: Thank you. Dr. Melish?

19 DR. MELISH: Well, I'm still a little  
20 confused about attributes and categories. We seem to  
21 be talking about both of them. I'm generally in favor  
22 of simplifying things.

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1 I would think that there are two  
2 categories maybe only that we need to talk about. One  
3 is the category about cleansing the hands of workers,  
4 and another category of preparing the skin for a  
5 surgical procedure.

6 I do think that the attributes should be  
7 different for both of those, because I think they're  
8 really quite different.

9 CHAIRMAN BRASS: Where would you put the  
10 consumer and home use in that spectrum?

11 DR. MELISH: The same as a caregiver and  
12 a food worker, I think, because they have the same  
13 needs. They want to cleanse their hands for a task,  
14 and they probably want it as broad spectrum as  
15 possible, because it's the same duty to your family as  
16 it is to your patient or your client in a food working  
17 situation.

18 CHAIRMAN BRASS: And you said the  
19 attributes would be quite different between those two  
20 classifications.

21 DR. MELISH: Could we talk a little bit  
22 about persistence. Given that, generally, the food

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1 worker -- particularly, the caregiver and maybe the  
2 food worker hasn't got as much need for persistence,  
3 because they should be washing their hands prior to a  
4 task, and will probably need to -- to be effective,  
5 will need to do it frequently because of the different  
6 things that they're doing.

7 They will contaminate their hands by  
8 seeing patients or picking up that chicken, and then  
9 they will need to wash their hands again. So they  
10 don't need so much persistence, and they probably need  
11 broader spectrum, because they have a lot of hazards  
12 that they are trying to mitigate; whereas, with the  
13 preparing of skin surface for, you know, safe surgery  
14 would really have a narrower range of pathogens that  
15 need to be treated for but a greater need for  
16 persistence.

17 CHAIRMAN BRASS: Thank you. Dr. Koda-  
18 Kimble.

19 DR. KODA-KIMBLE: I actually was taken by  
20 Dr. Larson's suggestion that we look at issues of risk  
21 as opposed to personnel. For example, an individual  
22 in a nurse or childcare situation where there was an

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1 outbreak of a certain condition or if you had an ill  
2 person in the house or if you had somebody who is  
3 susceptible to illnesses, might require a higher level  
4 -- I don't know what -- or some level of antisepsis  
5 and hand transmission than someone, for example, who  
6 uses it routinely for general hygiene, for example in  
7 the kitchen or in the bathroom or that sort of thing.

8 I do think the issue of skin prep is ,  
9 slightly different, just because of the resident  
10 organisms at the site. I do, though, think that time  
11 to kill should probably be the same for all of the  
12 products in any risk. It seems like you would want to  
13 get kill right away.

14 Persistence, I think, may not be an issue  
15 for health care workers, but I think would be an issue  
16 for any other situation that was high risk, because  
17 there's no -- It's unlikely that they would be washing  
18 their hands 30-50 times a day.

19 DR. LARSON: I'm not saying it may -- I  
20 think, you know, theoretically, it's a good  
21 characteristic to have, and I don't want to put us  
22 down going in the wrong way. I'm just saying we don't

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1 know, as far as I know.

2 If anybody here knows of studies that have  
3 shown added value to the characteristic of  
4 persistence, then I hope they will speak up.

5 I don't think -- I hate to see us go back  
6 and reinvent this entire thing again. I'm just asking  
7 if we could maybe simplify somewhere between what the  
8 TFM is and what the health care continuum model is. ,  
9 There's got to be some way.

10 Categories aren't as separate as we think  
11 they are. I'm not arguing for only two or three or  
12 any number. I don't want to put us down a path like  
13 that, but --

14 DR. KODA-KIMBLE: But I think we could  
15 think of many, many situations where an antiseptic  
16 would be required, where hand transmission is at  
17 issue. I think, if the panel or some group could  
18 define what those situations are where it's a health  
19 issue or a higher potential health issue, and if we  
20 could describe a product that meets -- that is likely  
21 to diminish risk of transmission, I think that would  
22 be very valuable to the public.

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1 DR. LARSON: Yes. An analogy would be the  
2 old isolation systems we used to have that were  
3 disease specific, like isolation for staph wound  
4 infection or whatever, to this new concept where you  
5 have certain precautions for everybody -- okay? --  
6 standard precautions, assuming everybody is infected  
7 with something that's potentially dangerous, and then  
8 you have levels, depending on the risk category.

9 So maybe a different way of looking at it,  
10 rather than the food service person, the health care  
11 worker might be much more helpful and will make more  
12 sense intuitively even to the consumer, and by  
13 consumer I mean all of us, not just the person in the  
14 home, but to all consumers.

15 CHAIRMAN BRASS: Dr. McKinley-Grant.

16 DR. MCKINLEY-GRANT: I must say, when I  
17 first started out with this, it was totally unclear  
18 what we were to do, but I feel like we're focusing a  
19 little bit more, and I feel like so much work has been  
20 done in these different areas about the studies, and  
21 we're not even at the point of talking about whether  
22 one product is better than the other. I mean, this is

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1 -- We know that they work, and I think we need to use  
2 that to our advantage.

3 I agree with Dr. Larson also in terms of  
4 looking at everyone as the same, you know, in terms of  
5 the potential for infection or for receiving  
6 infection.

7 The other thing that I am concerned about,  
8 though, is the viral coverage. I think we have a  
9 structure that maybe we could put antivirals in. I  
10 think it's a very -- you know, rather than going all  
11 the way back to base one to another monograph to, you  
12 know, 20 years later, it seems like we have a  
13 structure that maybe we could stick in antivirals  
14 here.

15 CHAIRMAN BRASS: Dr. Blewitt.

16 DR. BLEWITT: Well, just a couple of  
17 points here.

18 First, I think there's been general  
19 agreement, as I have seen it, that the testing  
20 criteria, as stated in the TFM, are not adequate to  
21 today's needs.

22 CHAIRMAN BRASS: We'll come back to the

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1 testing.

2 DR. BLEWITT: Okay. Although I just sort  
3 of wanted to comment on that, because it also concerns  
4 something else I'm going to say.

5 I think also that the health care  
6 continuum, as I see it anyway -- that it does  
7 demonstrate that there are differences in these  
8 products, particularly if you look at both ends of the  
9 spectrum.

10 I wouldn't consider a surgical scrub on a  
11 par with an antimicrobial hand wash or body wash. So  
12 I think that, although you can argue about how these  
13 things are classified, still I think there's a  
14 recognition of subtle or perhaps important differences  
15 in these products.

16 Having said that, I also get the sense  
17 that there are commonalities that exist as well in  
18 terms of criteria that you would establish for testing  
19 requirements, whether it's time to kill or things like  
20 that.

21 So there may be certain things that are  
22 common to all the categories, but there may be very

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1 different criteria for different categories as well.

2 So I would importantly ask that -- You  
3 know, as you recall, the TFM does not include consumer  
4 antimicrobials. I think it's important that these be  
5 put back into the monograph and that there be  
6 agreement that, however they are stated or however  
7 they are categorized, they do become a part of the  
8 monograph again, because right now they've been left ,  
9 out. Okay?

10 CHAIRMAN BRASS: Dr. D'Agostino.

11 DR. D'AGOSTINO: Yes. Could you state  
12 again what question I'm supposed to be answering?

13 CHAIRMAN BRASS: If I knew you were going  
14 to ask that, I would have waited until the very end to  
15 call on you.

16 We are addressing the general area of the  
17 impact of differentiation of intended use and  
18 attributes in classifying and talking about this broad  
19 group of agents. Is there value for differentiating  
20 them based on use, and how does that link to the  
21 attributes each use should have?

22 DR. D'AGOSTINO: I guess the answer is

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1 there are different uses, as we heard and so forth,  
2 and possibly developing tests that are getting into  
3 testing procedures that focus on those have some merit  
4 to them.

5 My general feeling is that we've heard  
6 this material a few times ourselves. It's not the  
7 first time that we've been presented with it, and  
8 there's quite a spectrum already. If you start now,  
9 taking the health care and splitting it up even  
10 further, which I think you, obviously, do in reality,  
11 but in terms of talking about procedures for testing  
12 and talking about giving some guidance to the FDA, I  
13 think it gets sort of overwhelming, that you get too  
14 particular.

15 I would argue that maybe we should realize  
16 that there are lots of sub-uses and what have you, the  
17 daycare, different hospital settings and so forth, but  
18 think more of the commonalities in terms of any  
19 recommendations we give.

20 I do want to -- I guess the next question  
21 is to talk about the particulars of some of those  
22 procedures.

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1 CHAIRMAN BRASS: Dr. Tong.

2 DR. TONG: I don't have a whole lot more  
3 to add to what I've heard. I do want to get into the  
4 discussion about the particulars.

5 I think the point that was mentioned about  
6 consumer monographs makes sense, because if we're  
7 going to address the attributes by looking at risk  
8 characteristics versus the individual use situations,  
9 that's going to bring in how we deal with consumer and  
10 the information that's going to be conveyed to a  
11 patient -- or a consumer, I'm sorry -- you know,  
12 dealing with things like viruses.

13 CHAIRMAN BRASS: We're not going to  
14 reimburse you for the cost of that.

15 DR. TONG: No, but I was curious to see  
16 what was out there. As you know, all of us in the OTC  
17 business often are amazed at what goes on.

18 I think, you know, this is going to be  
19 something that is worth looking at, and I do agree  
20 that I didn't find much discussion in the TFM on the  
21 antibacterial -- or antiseptic body washes and hand  
22 washes, and actually, I was reassured when Dr. Leyden

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1 made some, I think, very valuable, helpful information  
2 to me in terms of what happens to the patient out  
3 there, not the individual where decisions are already  
4 made about what to buy for the surgical suite or for  
5 the unit ward or for the childcare center.

6 It's the individual who goes to CVS and  
7 finds this on the shelf. So I think a lot of work has  
8 been done, and I like the idea of -- maybe simplifying,  
9 isn't the correct word, but the TFM was getting off  
10 the drawing board in 1994.

11 I thought the health care continuum model  
12 was an extremely good response to what came off the  
13 drawing board, and this is still the process of  
14 looking at those, at both points of views, and coming  
15 to something that would be useful, but it's reassuring  
16 to know that we're really talking about products that  
17 do work. There are just differences, and the  
18 differences could be applied to the risk application  
19 of these products. I think that's where the work is  
20 going to be.

21 CHAIRMAN BRASS: Dr. Gilliam.

22 DR. GILLIAM: I'd like to echo Dr. Tong's

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1        comments with respect to the consumer.    I think  
2        there's a lot of confusion out there as to what the  
3        words antibacterial on Lever or on Dial or whatever  
4        means, and what exactly are they getting for that  
5        money that they spend versus a regular hand soap or  
6        whatever.

7                    There have been reports, at least in the  
8        Tucson newspapers recently by Dr. Gerber who is one of  
9        our faculty members, who has done cultures all around  
10       the home, toilet seats, etcetera, and then he's used  
11       actually diluted bleach solutions and found how much  
12       they reduce bacteria in the home and instance of viral  
13       infection and everything, too.

14                   So I think there's confusion on the part  
15       of consumers as to what exactly antibacterial means.  
16       Does that have like a hospital or a medical standard  
17       implied in it?

18                   I very much like the idea of going with  
19       looking at risk uses of these different products.

20                   CHAIRMAN BRASS:        Thank you.        Dr.  
21       Krenzelok.

22                   DR. KRENZELOK:    Thank you.    This has been

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1 most interesting. I certainly feel like a fish out of  
2 water with my toxicology background, to a certain  
3 extent.

4 So I'd like to turn the table just a  
5 little bit so I can use the little bit of that and  
6 talk about risk. I agree very much with Dr. Larson in  
7 focusing that risk, and I think that we ought to  
8 consider at least narrowing these categories and ,  
9 narrowing the focus just a little bit; because it's  
10 quite confusing with all these different categories,  
11 I think.

12 Somewhere in our packet of information  
13 there was a quote that was attributed at least to  
14 Paracelsus. Basically, what it said was the only  
15 thing that differentiates a poison from a remedy is  
16 the dose.

17 A lot of these things are ubiquitous in  
18 our home environments and hospitals and so on, but  
19 especially, as Dr. Tong was saying, being more  
20 consumer oriented, these things are in the home.  
21 These types of products are really the most common  
22 type of thing that little children get into, for

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1 example, as a common exposure agent.

2 Now in looking at these particular agents,  
3 whether it's chlorhexidine or some of the others,  
4 they're pretty safe. I think we're pretty confident  
5 about that. You don't have to worry about  
6 methemoglobinemia from the conversion of the  
7 chlorhexidine to the parachloranalin and things of  
8 that nature.

9 We might have to be concerned about the  
10 cationics, if these -- and I don't know exactly what  
11 products we'll look at, but the cationics, I think, do  
12 certainly pose some particular problems.

13 So I'm a little bit troubled by that, but  
14 a comment that was made this morning, I think, perhaps  
15 troubled me just a little bit more, and it had to do  
16 with the irritation potential.

17 Throughout the TFM it talks about the  
18 products should be nonirritating in each and every one  
19 of those categories. I think -- and correct me if I'm  
20 wrong, but I think I heard one of the speakers say  
21 this morning that they let the marketplace really  
22 dictate what's irritating and what isn't.

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1           I think that one of the things that we  
2   ought to be is more responsible and more proactive in  
3   determining what's irritating up front than what's  
4   irritating after it hits the marketplace. I don't  
5   think that's a very positive way to approach products  
6   like this.

7           If we want to enhance compliance, we want  
8   people to wash their hands for 20 seconds or for ten  
9   seconds or 18 times a day, if it's irritating, they're  
10   not going to use it. So I think that should be  
11   something that we should take on very proactively.

12           Something else that concerned me just a  
13   little bit this morning, looking at sort of our era of  
14   evidence based medicine in the nineties, I was a  
15   little troubled about what really constitutes an  
16   endpoint here.

17           If we've reduced the bacterial flora by 2  
18   logs, you know, what's the threshold? What's good?  
19   What will basically decrease the risk of transmission,  
20   as Dr. Koda-Kimble was saying? What is that  
21   concentration, and I realize that gets into testing  
22   and a variety of issues, but I really feel confused

1 about that, and I don't think that we ought to be sort  
2 of led down the path of thinking, just because it  
3 reduces bacteria by 50 percent or by 60 percent, that  
4 it reduces risk by that much.

5 I don't think we can correlate the amount  
6 of flora that's left or amount of bacteria that are  
7 left with risk reduction.

8 So those are some things that come to mind  
9 that are a little bit troublesome, that I think need  
10 to be thought through a bit. Thank you.

11 CHAIRMAN BRASS: Thank you.

12 DR. BLEWITT: I just wanted to make one  
13 quick comment about one of the statements regarding  
14 irritation this morning and what I heard and what I  
15 think was intended by it.

16 I think any company that I've ever known  
17 of, including the ones that I've been associated with,  
18 will always do some sort of battery of irritation  
19 testing for any of its products. Have to, absolutely.  
20 But these panels are often of such a size that you  
21 really may not know the overall potential for  
22 irritation until there is wide scale use of them.

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1 I think that that was really what that  
2 comment addressed in terms of the marketplace driving  
3 that particular criteria.

4 CHAIRMAN BRASS: Dr. Neill.

5 DR. NEILL: I agree with Dr. Larson that  
6 the number of categories here seems somewhat  
7 artificial and based on the market or use rather than  
8 the particular characteristics of the products that  
9 we're discussing, and so would favor a labelling or  
10 approval process that focused on the characteristics  
11 of the products and allow the labelling to reflect its  
12 efficacy vis a vis this particular characteristic,  
13 whether it's onset, persistence, etcetera.

14 The only other comment I guess I'd make is  
15 that, as we begin to talk about testing, it's clear  
16 that many of the tests that are in the TFM don't  
17 reflect actual use inasmuch as we don't wash our hands  
18 for 30 seconds. I tried at lunch. Couldn't do it.  
19 Got bored, and I couldn't remember the words --

20 DR. LARSON: You can do it if you're  
21 watching TV.

22 DR. NEILL; There's a thought. Put TVs on

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1 all the wards.

2 So I do think some thought needs to be  
3 given to revising the tests to reflect actual use,  
4 such that the characteristics that we define or that  
5 we choose can be tested in a way that will result in  
6 an effect when used, which is advertised. You know,  
7 my product is persistent as used, and that's what's  
8 seen when you buy it and stick it on your shelf at  
9 home or in the hospital or use it for whatever you  
10 plan to use it for.

11 CHAIRMAN BRASS: Please, Dr. Gilliam.

12 DR. GILLIAM: I want to make just a  
13 comment, throw out something about hand washing. You  
14 know, we're debating ten seconds versus 20 seconds  
15 versus 30 seconds. My kind of way of thinking about  
16 this is that, while you say that you're supposed to  
17 hand wash for 30 seconds, you might only do it for 15.  
18 So you're still getting to where you need to go.

19 Then what if we say, well, you're supposed  
20 to hand wash for 15 seconds. Do then people start  
21 saying, well, they say 15, and the only -- that means  
22 we only have to wash our hands for five seconds, and

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1 that that will be enough?

2 That's, you know, kind of my concern about  
3 that thinking, is that, you know, if we keep lowering  
4 the limits, then people are going to say, well, we  
5 really don't need to wash our hands that much. So we  
6 won't -- we'll get to the point where we're  
7 essentially just passing them through the water, and  
8 that might be it.

9 So that's my concern with hand washing  
10 there.

11 CHAIRMAN BRASS: Dr. Larson?

12 DR. LARSON: I think this is an example of  
13 getting mired down, to some extent. Not that it's not  
14 important. It is, but there have been studies, as I  
15 said, for example, to show that ten seconds is the  
16 same as 15. Okay.

17 The thing is -- and we know that our  
18 outcome, our objective, is reduction in infection. We  
19 know that, and we're not there totally with evidence  
20 for that, and some of these things -- I think this  
21 committee is going to have to just decide what is a  
22 reasonable expectation to demonstrate that what goes

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1 out in the market is safe and efficacious to the  
2 extent that we know, given right now, and then let's  
3 just keep, you know, the work coming.

4 In some ways, it's almost better to get  
5 this thing finalized than to go another decade waiting  
6 for the clinical trials that will be the definitive  
7 trials. It seems to me that just a reasonable,  
8 reachable standard to demonstrate that there is a good  
9 product and a bad product, and that the good product  
10 meets a certain -- is in a certain category for use.

11 That would be great, and that's sort of  
12 all this group can do right now.

13 CHAIRMAN BRASS: I personally think that  
14 much of the problem we have coming to grips with this  
15 is because of the -- and the word continuum in the  
16 model proposed by the coalition is appropriate,  
17 because there's absolutely a continuum of indications.

18 You can make it five. You can make it 55.  
19 You can make it 55,000, if you try to define the  
20 different uses. But at the same token, I think it  
21 makes intuitive sense, even in the absence of data,  
22 that the characteristics to prep a patient for surgery

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1 are different than what the average American household  
2 needs to wash their hands with, and that in the  
3 absence of such additional information, it's hard.

4 If you take the analogy to classical  
5 products, no drug antibacterial would be approved  
6 simply because it killed bugs. It would require an  
7 indication to be used, and whether or not that was  
8 meningitis, pneumonia or whatever would make a very  
9 large difference in how that drug actually reached the  
10 marketplace.

11 It seems to me, we're at the stage of  
12 defining what is an antimicrobial, what is an  
13 antibacterial, and not what the indications for their  
14 use are; because, in fact, the data for the  
15 indications for the use, which we're going to talk  
16 about in the testing, may be very, very different, but  
17 in ways we can't fully define yet.

18 I think the other point that was made, and  
19 I think there would be consensus about -- so I just  
20 want to reiterate it -- is that linking -- making  
21 pathogen synonymous with bacteria has to stop, and  
22 that what we're talking about in these agents is the

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1 full spectrum of infectious agents, not just viruses  
2 but coming from Harbor, mycology is kind of important.  
3 So candidal infections are very important, and as  
4 parasitic infections will be in certain select  
5 populations.

6 So I think that, when we talk about  
7 spectrum -- and that will be linked to the specific  
8 indication as to how important that is, but I think  
9 that goes without saying.

10 So I think, from that framework, we can  
11 now begin, if it's okay with the agency, to begin  
12 talking about some of the specific testing  
13 methodologies and how some of the things we have heard  
14 and discussed would interface with that kind of  
15 intended use framework.

16 Dr. Larson, would you be so kind again?

17 DR. LARSON: You want to talk about  
18 specifics?

19 CHAIRMAN BRASS: Any issues that you feel  
20 in the area of testing methodologies, hopefully not  
21 focusing on the number of seconds of hand washing but  
22 thematically and conceptually that are important to

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1 incorporate into this rulemaking process.

2 DR. LARSON; Well, let me start with a  
3 general comment I made before. That is that the  
4 problem with the old TFM from '74 is that there were  
5 no controls. There were no standards against which to  
6 compare.

7 Now we solve that problem, but what is the  
8 most important clinical organism or -- not even the  
9 most important clinically. What if we find out that  
10 something is better than Serratia? Okay.

11 Why do we have to be so prescriptive in  
12 some ways? I understand there -- What's the fine line  
13 between comparability and flexibility that is needed  
14 for some of this testing? I mean, just for starters,  
15 where is the test for the waterless products, and how  
16 do they merge with those E-1, E-2 things from the food  
17 handling stuff, which is a whole different testing  
18 thing?

19 Those somehow, it seems to me, have to be  
20 merged.

21 CHAIRMAN BRASS: If I could just follow up  
22 briefly on that flexibility point, because I think

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1 it's very important. I think that, given particularly  
2 the expectation for innovation in the marketplace and  
3 by industry to preclude an innovative product having  
4 a different prescription for use, for example, that  
5 might only require three seconds of hand washing or  
6 perhaps for a special indication 60 seconds of  
7 intensive preparation would be ridiculous to remove  
8 the flexibility from a sponsor to develop innovative  
9 products with innovative uses.

10 I know the TFM does say "or as described  
11 by the sponsor" in those testing, and I just want to  
12 reiterate that. Is that what you were going to say?

13 MS. LUMPKINS: Well, beyond that, one of  
14 the things that I was going to point out is: One of  
15 the reasons that we went with such prescriptive  
16 protocols in the TFM is we wanted -- Everybody in this  
17 room knows that the way you conduct the test impacts  
18 on the results that you get.

19 We were looking for some commonality of  
20 procedure so that, when you grab the product from the  
21 shelf, you would know it had been tested in a  
22 particular way, and that they had all been tested that

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1 way.

2 So I'm not adverse to flexibility, but  
3 there is -- there was that intent.

4 CHAIRMAN BRASS: Yes, but that's not a  
5 philosophically different thing that we usually deal  
6 with. If a sponsor wanted to make a claim that a drug  
7 was effective against ulcers, you would make some --  
8 there would be some standard ways of doing it, but if  
9 an individual sponsor had an innovative way of  
10 demonstrating efficacy, the agency historically has  
11 worked with sponsors to -- and I realize the scope of  
12 this is much larger, but I think the concept that  
13 working with more innovative ways of dealing with it  
14 is at least as important; because I think what a  
15 consumer or the user is going to care about is whether  
16 the claim is legitimate, not whether the claim was  
17 verified in exactly the same way as the product on the  
18 next shelf.

19 DR. LARSON: I mean, we can start with the  
20 easy things, like the new tools. Everybody, I think,  
21 is pretty much in agreement there's an issue there.  
22 Another easy thing is that, for the application, let's

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1 say, whatever you end up calling the health care  
2 personnel hand wash application, i.e., an antiseptic  
3 use in a high risk situation, that it should be closer  
4 to real life use like maybe 15 seconds or whatever.

5 Let me just ask, what if a manufacturer  
6 wanted to make the claim that their product does in  
7 five seconds of contact time what the other products  
8 do in 30 seconds? How could they do that? They  
9 couldn't get -- It couldn't happen.

10 It would be a great -- I mean, talk about  
11 risk/benefit and cost/benefit ratio. If we could find  
12 something that would work in five seconds instead of  
13 30 -- There have been studies published that show  
14 that, if people actually washed their hands as often  
15 as CDC says they're supposed to, they wouldn't have  
16 time for any patient care, and they wouldn't have any  
17 hands left.

18 So anything we can do to reduce the time  
19 and the numbers of applications, the better. Yet  
20 there's no way for a good company to make a claim  
21 outside of the monograph claim. So that means in 30  
22 seconds it works.

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1 CHAIRMAN BRASS: Dr. Katz?

2 DR. KATZ: Well, there actually are other  
3 ways outside of the monograph to make claims.

4 DR. LARSON: Maybe that's in the NDA  
5 process.

6 DR. KATZ: That would be through the NDA  
7 process. So that, looking at the monograph, what  
8 you're trying to do is to try to make sort of a level  
9 playing field in the sense that this is a standard  
10 that everyone should be able to meet -- to be able to  
11 make to get the claims that the monograph would set  
12 forward.

13 For an NDA that would be the time to make  
14 some innovative claims which that particular product  
15 may be the only one that could do or NDA deviations to  
16 the monograph and things along those lines.

17 So there are other options within the  
18 regulatory framework of the agency to allow for that.

19 DR. LARSON: Sure. It just seems to me  
20 that there may be things that are now under the OTC  
21 that could make other claims, but -- well, anyway,  
22 your point is well taken.

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1           If nothing else, then we should have it  
2       not 30 seconds then for -- We should have it 15,  
3       because no use being able -- I agree with the level  
4       playing field, but nobody is going to use it that way  
5       in real life.

6           DR. KATZ:   That's actually why we're  
7       bringing some of this back up, because as you've even  
8       heard from this morning with the discussion is that,  
9       when the original 1974 document itself didn't allow --  
10      it was too vague.   The 1994 document may be too  
11      specific in certain areas so that the standards are  
12      such they can't be met.

13          DR. LARSON:  Now the next question is --  
14      Let's say that, as two people have suggested, the  
15      consumer products be added again to the TFM.  Then if  
16      they're going to be used in a different way -- One of  
17      the problems now is do they have to pass the rigid  
18      health care personnel hand wash protocols, and that  
19      doesn't seem reasonable.

20          CHAIRMAN BRASS:  Thank you.  Dr. Rice?

21          DR. RICE:  I think I have maybe just a bit  
22      more to add.  I tend to concur, we need to, if I

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1 understand what I'm hearing, establish and adhere to  
2 some minimum standards for compliance criteria, but  
3 relative to the prior discussion in terms of risk  
4 categories, I think there needs to be flexibility in  
5 terms of the monograph and standards so that we can  
6 address new and emerging pathogens as well as consumer  
7 and population and perhaps new environmental  
8 challenges, so that we're able to entertain more  
9 innovative and newer claims.

10 That's what I would like to add to the  
11 conversation, but I would tend to concur with the  
12 prior comments.

13 CHAIRMAN BRASS: Thank you. Dr. Melish.

14 DR. MELISH: I have no more to add at this  
15 point.

16 CHAIRMAN BRASS: Thank you. Dr. Koda-  
17 Kimble?

18 DR. KODA-KIMBLE: I'm going to forget  
19 which organization it was, but it's AT -- the testing  
20 group? ASTM? Okay.

21 I don't know about this group, but if it  
22 truly is a peer review group that consistently and

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1 over time evaluates testing methodology, I wonder if  
2 we could adopt some language that refers back to a  
3 standardized procedure that is accepted by the  
4 industry as a way of evaluating whatever it is we're  
5 going to evaluate, time to kill, persistence,  
6 antimicrobial activity, spectrum of antimicrobial  
7 activity.

8 One of the things I did notice in the  
9 comments was that there was deviation from those  
10 standards and that, in fact, the technology had  
11 changed over time, and it probably still will. So it  
12 ought to be a living document, something that reflects  
13 current reality, as we learn more information.

14 CHAIRMAN BRASS: Dr. McKinley-Grant?

15 DR. MCKINLEY-GRANT: Okay. I basically  
16 agree with all the comments. I just wanted to add  
17 that -- and to stress that I think any studies that  
18 are done should be actual use studies of, you know,  
19 hospital patients, of food handlers, of food workers,  
20 of daycare, to try to really get actual use.

21 The other thing is dermatologists. If you  
22 could include diseased skin and normal skin in some of

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1 the studies, I think that would answer -- help to  
2 answer some of the questions about irritation and who  
3 can actually use some of the products.

4 CHAIRMAN BRASS: Dr. Blewitt.

5 DR. BLEWITT: Again, I think -- and I  
6 think Dr. Larson just sort of emphasized the fact that  
7 testing criteria should be specific to the specific  
8 product category in citing the difference between  
9 health care hand washes and consumer hand washes.

10 I, frankly, think that this particular  
11 subjects gets to the point where the details go beyond  
12 the scope of this group to handle. My suggestion  
13 would be that there be some sort of continuing  
14 dialogue to hammer out the details of the testing  
15 requirements with the appropriate interested parties,  
16 industry, FDA, whether it involves ASTM or whoever,  
17 that that is the way that it is eventually resolved.

18 CHAIRMAN BRASS: Let me, since you raised  
19 it, ask you, but asking the panel, a rhetorical  
20 question in response to that. I agree that it's  
21 probably inappropriate for us to pick a kill level  
22 today --

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1 DR. BLEWITT: Right. How many seconds.

2 CHAIRMAN BRASS: -- to be on page 342 of  
3 the monograph. However, I would ask you, what  
4 information would you like available to set an  
5 appropriate kill level for efficacy for a consumer  
6 product?

7 So in other words, if -- We're talking  
8 about claims being made. If somebody was to claim --  
9 don't worry about what it met, but if they wanted to  
10 say they could claim that their consumer product  
11 killed bacteria on the skin.

12 DR. BLEWITT: All right.

13 CHAIRMAN BRASS: If it killed one  
14 bacteria, would that be enough for the claim? How  
15 would you suggest that information be processed to  
16 allow a decision to be made without having access to  
17 the --

18 DR. BLEWITT: Well, you would have to look  
19 at the database and the sufficiency of the database in  
20 terms of how much direction you get from that, and  
21 that would include both published literature and any  
22 data contained within companies that they're willing

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1 to share.

2 Then -- One of the ways I sort of look at  
3 this is statistical versus clinical significance.  
4 What is meaningful? I think that probably those who  
5 are best educated in that process, probably a  
6 combination of people who are basic scientists and  
7 clinicians, can try to hammer something like that out.

8 Does that answer your question?

9 CHAIRMAN BRASS: Again, it wasn't a  
10 question just for you. It was a way to try to help  
11 add some focus here.

12 Dr. D'Agoscino?

13 DR. D'AGOSTINO: I guess I always feel  
14 like I'm missing the discussion. I mean, I'm not  
15 convinced that we really have a sense of endpoints,  
16 for example. I mean, are all the in vitro, in vivo --  
17 that's what I thought that we were going to be asked.  
18 Is this whole plethora of in vitro and in vivo tests -  
19 - is that really sensible, this long list of  
20 organisms?

21 CHAIRMAN BRASS: Feel free to answer that  
22 question.

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1 DR. D'AGOSTINO: I'm asking him. You  
2 know, is that sensible? I thought that's what we were  
3 going to sort of grapple with. Is this strategy the  
4 right strategy? I'm not saying it isn't the right  
5 strategy. I just don't know if I've heard enough  
6 presentations today and I've read enough to be able to  
7 answer that question.

8 Some of the comments that you were just  
9 making -- I mean, it's another body of scientists and  
10 experts that would have to help us. I do have very  
11 strong opinions about the clinical trials.

12 I mean, I spend a lot of my life looking  
13 at cardiac problems and cancer problems and so forth,  
14 and they have no problem putting clinical trials  
15 together. Here it's kind of hard to be told that hand  
16 washing is so overwhelming that we can't put a  
17 clinical trial together. I mean, I --

18 DR. LARSON: No. I don't -- I think the  
19 problem is that, with surgical site prep, you can.  
20 With other things, you can. You probably can with  
21 hand washing. Brad Demeling got a good start on it,  
22 and there are some people who are doing it, but it is

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1 a little bit harder to control all the confounding  
2 variables. It's a complicated study. I agree.

3 DR. D'AGOSTINO: You know --

4 DR. LARSON: All I'm saying is this  
5 committee shouldn't wait for a definitive clinical  
6 trial on every application of hand washing with the  
7 outcome being infections, because, you know, that will  
8 be here another 40 years for every --

9 DR. D'AGOSTINO: Well, you know, maybe 20  
10 years ago somebody said that question would have  
11 something going now and so forth. I think we  
12 shouldn't wait forever also, but I don't think that we  
13 should just say, because it's going to take a while,  
14 that we shouldn't raise the discussion and then ten  
15 years from now somebody else raises the discussion.  
16 They say, well, you know, it's going to take a while.

17 I think the discussion should be raised  
18 now, and certainly, I think that we should make  
19 recommendations or at least get my voice into it. I  
20 think clinical trials are definitely essential and,  
21 knowing this, I think we need to know what the  
22 endpoints are, and we need to design clinical trials

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1 according to those endpoints.

2 I do think I'd like to hear some more  
3 about these in vitro, in vivo tests and just how  
4 useful they are. How do they add? How do they  
5 substitute for in-use? I mean, are we really saying  
6 that, if you do enough of these, you don't need to do  
7 in-use or actual use studies, intended use?

8 I haven't heard that discussion. I really  
9 would like to hear that discussion. I don't think  
10 that there are substitutes for them.

11 CHAIRMAN BRASS: Dr. Tong -- or Dr.  
12 Blewitt, did you want to add?

13 DR. BLEWITT: I was just going to comment  
14 -- respond to that comment, which I think certainly  
15 has a great deal of merit.

16 One of the ways I look at this, as I look  
17 at this health care continuum model, is that -- and  
18 look at the population impact as you go from pre-op  
19 skin preps up to antimicrobial body wash, the  
20 population impact becomes greater and greater, and I  
21 think the way I look at it, the greater the population  
22 impact, the more difficult it is to do any kind of

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1 controlled clinical trials.

2 It's perhaps much easier in a hospital  
3 setting than when you try to look at the impact of  
4 hand washing on the general population. How do you  
5 design any kind of trial that would define those  
6 performance characteristics?

7 So I think, as you get out into larger  
8 populations, it becomes much more onerous.

9 CHAIRMAN BRASS: Dr. Tong?

10 DR. TONG: I don't have anything to add.

11 CHAIRMAN BRASS: Dr. Gilliam?

12 DR. GILLIAM: Nothing further.

13 CHAIRMAN BRASS: Dr. Krenzelok?

14 DR. KRENZELOK: One final comment. I  
15 heard the term broad spectrum bandied around quite a  
16 bit this morning, and one of the speakers this  
17 morning, I thought, sort of put some focus on that and  
18 basically said that we ought to be performing testing  
19 based upon the organisms that you're most likely to  
20 encounter, rather than a potpourri of organisms that  
21 are just there for the sake of testing.

22 As I looked at the proposed rules, there

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1 are 20 different organisms, including candida, and  
2 perhaps a group with the specific expertise of saying,  
3 okay, these are the 14 organisms or the five organisms  
4 we should use should be -- this should be referred to  
5 them to get some better guidance and provide better  
6 direction along those lines.

7 CHAIRMAN BRASS: I think that's right. I  
8 think this goes back to the indication specificity.  
9 I mean, to have an indication for daycare center  
10 workers that doesn't include viruses doesn't make any  
11 sense.

12 DR. KRENZELOX: Exactly. I agree entirely  
13 with that.

14 CHAIRMAN BRASS: Dr. Neill?

15 DR. NEILL: Just a few comments,  
16 specifically about the recommended revisions in the  
17 testing that came from the CTFA. I don't remember  
18 what the acronym stands for, but from industry.

19 A couple of the specific alterations to  
20 the tests raised questions in my mind, to begin with.  
21 In the preoperative skin preparation category, one of  
22 the tests for establishment of the activity of the

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1 product and its ability to show a log decrease  
2 suggests that, if you begin with the FDA starts with  
3 on the abdomen and groin, there's not enough. So  
4 let's put some more bacteria there, and then we'll be  
5 able to show a reduction.

6 That troubles me a bit, and specifically  
7 on page 29, footnote 2 to their table, they suggest  
8 this, also on page 26 earlier in the body of their  
9 text. I guess, because adding bacteria to the skin is  
10 going to -- as part of the testing process.

11 What I've heard today suggests to me that  
12 I would be able to show a reduction in that anyway.  
13 Put bacteria on the skin. It's going to go away. So  
14 I think that this more speaks to the question of  
15 whether or not we have any adequate handle on log  
16 reductions, to begin with, and is this a reasonable  
17 test.

18 I interpret this suggestion from the  
19 consortium more as an effort to come up with  
20 something, and I think maybe it was just unreasonable  
21 to have something, to begin with.

22 Second, a couple of people have raised

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1 issues about the consumer use for these things, and  
2 there's a comment in the consortium information that  
3 I received on page 60, which suggests that they've had  
4 difficulty providing the FDA with data regarding the  
5 efficacy of their consumer products, because they  
6 won't share their data with one another by virtue of  
7 combining -- to form some joint set of  
8 recommendations.

9 I'm not sure that that's going to change,  
10 regardless of what we say. So I'll just throw that  
11 out there. If we decide there are some tests that we  
12 want the FDA to apply for claims related to product  
13 use in the consumer arena, we may have to do that  
14 without data from products that are already there.

15 Then lastly, just not related specifically  
16 to the question of tests and testing, if the process  
17 that we're undergoing now is to advise the FDA  
18 regarding claims related to the labelling of some of  
19 these products, then given that we're dealing with  
20 antimicrobials to be used in a variety of settings,  
21 the questions that run through my mind are: if there  
22 are some very nonspecific claims that are made or, for

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1 that matter, very specific claims -- this will reduce  
2 bacterial colony counts -- I guess I would urge that  
3 the tests be specifically related to the claim, such  
4 that when we begin to see claims made to the hospital  
5 formulary committee in deciding what to stock in its  
6 operatory, this reduces the rate of post-operative  
7 wound infections in hip surgery, that we have some  
8 reason to be able to judge that claim.

9 I think that the Chair has already made  
10 that point by saying that we could be here forever and  
11 never define all of those, and perhaps that speaks to  
12 the need for flexibility. However, given the criteria  
13 that are in the TFM in terms of persistence, onset of  
14 action, which may or may not have relevance to  
15 clinical efficacy in the specific conditions that we  
16 think these products are going to be used for, food  
17 borne illness and rates of attacks and such, with  
18 relation to those specific characteristics it seems  
19 like there are some criteria. They're there.

20 The main objection I heard this morning  
21 was that none of the products can meet some of them.  
22 Gee, you know, if they're not related to clinical

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1 activity or clinical efficacy anyway, I don't have any  
2 problem with changing them, because they may be  
3 meaningless. But if the point is to have some test  
4 that serves as a surrogate, then choose one.

5 I'm not in the business of excluding  
6 products from the market. On the other hand, it  
7 sounds like we are in the business of making sure that  
8 the claims that are made bear some relation to reality  
9 and need to be fairly specific.

10 CHAIRMAN BRASS: Thank you. I -- Yes?  
11 Please identify yourself.

12 DR. RESH: I'm Carol Resh from Unilever.  
13 I've worked with the coalition now for four years,  
14 since we started, and I just wanted to comment,  
15 really, on two of the things that you've said.

16 One was about the patient pre-op procedure  
17 and adding bacteria. We didn't actually suggest you  
18 add bacteria. The clinical procedure as put forth in  
19 '94 suggested that you have numbers that just aren't  
20 found, and I think Gale Mulberry is here from Hilltop,  
21 and he can tell you, you can't find people that have  
22 numbers that high.

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1           So we either said you included it to  
2       increase the natural flora by occlusion, which I think  
3       Jim showed you earlier will increase the numbers; and  
4       we weren't suggesting that you really wanted to add  
5       bacteria. It's just that, in order to get the number  
6       up there so you can get it, you have to do something,  
7       because that number just doesn't exist. Gale can  
8       speak to that.

9           CHAIRMAN BRASS: Again, please identify  
10      yourself.

11           MR. MULBERRY: Gale Mulberry with Hilltop  
12      Research, testing laboratory.

13           The pre-op skin prep -- we've found  
14      difficulty particularly in -- This is not on --  
15      predominantly on the abdominal sites finding counts  
16      that are at the level specified in the monograph.

17           Maybe about 20 percent or maybe only 15  
18      percent of the subjects that we looked at on the  
19      baseline counts have organisms in that level. So that  
20      means, to find a panel of 30 subjects, we would have  
21      to screen two, three, 400 people.

22           It seems unrealistic, because it's not

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1       reflective of what's normally in that area.

2               DR. NEILL: I guess, as I read that -- not  
3       to interrupt, but to do exactly that, interrupt --  
4       another way to interpret that or another way to make  
5       a different recommendation could have been lower the  
6       initial colony counts that we find to something that  
7       we actually see in real life, but have a similar log  
8       reduction, which I expect would be a more difficult  
9       standard to meet, and maybe impossible like some of  
10      the others that we have already seen may be impossible  
11      to meet.

12             MR. MULBERRY: For the abdominal site, it  
13      doesn't seem reasonable to raise the population to the  
14      level just to meet the log reduction. It seems like  
15      we should be looking at a different criteria, a  
16      different log reduction.

17             DR. LARSON: Could I just add -- Gale and  
18      a number of us, and I was there as a, I guess,  
19      researcher/clinician -- Years ago there was an FDA  
20      group that was convened to talk about the testing  
21      standards for pre-op skin preps, and I don't know  
22      whatever happened. But all of us were saying the

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1 standards are unrealistic and, in order for industry  
2 to respond with a test that will meet those standards,  
3 they have to create other artificial things like, you  
4 know, occlusion to grow up enough bacteria or to  
5 screen hundreds of people.

6 So the problem is getting the standards so  
7 that they're doable and relevant. That was at least -  
8 - I think it was close to ten years ago. Nothing's  
9 happened. So I'm expressing my frustration, because  
10 we have been consulting on this, and now, you know --  
11 I agree that we need to go back and use experts or  
12 whatever, but we've been, you know, trying to get  
13 these things changed.

14 We've been trying to define relevant  
15 clinical outcomes, both endpoints and appropriate  
16 surrogate, you know, measures that have sufficient  
17 sensitivity and specificity, because you always have  
18 to, you know, kind of dance with that one a little  
19 bit.

20 So I don't want us to end up at the end of  
21 the day where we are at the end of every one of these  
22 meetings I've been to.

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1 CHAIRMAN BRASS: We agree. Dr. Tong?

2 DR. TONG: I just wanted to add to Dr.  
3 Larson's comment about realistic standards, and I'm  
4 sitting here thinking about food handlers and feeling  
5 that we hold the performance expectations of food  
6 handlers, products used by food handlers fairly high,  
7 and it's very rigorous, because there's a number of  
8 other things that go along with the use of antiseptic  
9 washes -- hand washes before food preparation.

10 I'm extending that to consumers. We talk  
11 about, well, you know, it's just on the risk and leave  
12 the different categories out, and would it be  
13 realistic to apply those same standards and say, you  
14 know, this is a product for consumers.

15 We know that in poison centers we don't  
16 get outbreaks of food borne illnesses in public places  
17 as often as we get the home situation. I mean, that  
18 far outnumbers probably nine to one in terms of, you  
19 know, how frequent.

20 I don't have an answer to this, but I'm  
21 just thinking as the discussions go on at the agency  
22 level and in industry, one of the things that I think

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1 we'll have to deal with is realistic standards. I'm  
2 just thinking about the food handling issue, you know,  
3 and how that's going to be handled in a consumer frame  
4 and how that's going to be addressed.

5 CHAIRMAN BRASS: Yes.

6 MS. RESH: Carol Resh, and I'll just  
7 finish my other point before we get too far. When we  
8 started -- The document you saw was something we  
9 wrote, I guess, January of '95 -- '96. Subsequent to  
10 that -- '95? '95, time flies.

11 Subsequent to that we did submit to the  
12 agency blinded company data. Yes, we do have a  
13 problem sharing our data among such divergent  
14 companies. We have recognized we're in all of these  
15 categories. Some of us are more willing to share our  
16 data than others.

17 So we blinded it, and we have now  
18 submitted another 16 volumes or something to Debbie  
19 and to the docket that has a lot of the -- a  
20 tremendous amount of the in vitro data and the in vivo  
21 data.

22 We went back. We pulled all the published

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1 literature we could find, put it in the same format.  
2 That's one of the things we had, is everybody sends  
3 their data their special way. So we put it all in the  
4 same format. So we have submitted data. There is  
5 plenty of data in the docket.

6 I think we just need to move on. If we do  
7 need to generate data, we need to know from the agency  
8 what we should do, because at this point we don't want  
9 to be generating data that they're going to say, well,  
10 you didn't write it the way we want it. We need to  
11 know specifically what they're looking to.

12 DR. HAAS: Chuck Haas. I want to tie  
13 together two things that I thought I just heard.  
14 First of all, discussion on log reduction -- I  
15 understand why that originates, coming from a  
16 disinfection background, but Paracelsus was mentioned  
17 earlier.

18 The dose does make a poison for  
19 microorganisms as well as for chemicals, and in all  
20 the dose response modeling we've done, we have not  
21 found any evidence for threshold for any organisms.

22 I would submit to you then that it may

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1 very well be the endpoint microorganism concentration  
2 rather than the logs reduction taken to get there  
3 that's indicative of the ultimate risk.

4 One possible alternative that might be  
5 considered is to focus attention not simply on log  
6 reduction but on ultimate endpoint count.

7 CHAIRMAN BRASS: Thank you. Please?

8 MS. BRECK: I'm Mary Breck, and I'm a  
9 consultant. I think probably with a few others in the  
10 room, I have a record of being involved with this. I  
11 was the Executive Secretary for the original panel.

12 I wanted to answer Dr. Larson's question  
13 about where we are with the alcohol product and a test  
14 method for that. ASTM -- I hope we are in the last  
15 ballot round with a test method based on Dr. Rotter's  
16 hand rub and also on the CEN, which is the European  
17 standard for hand rub.

18 So there will be a published test method  
19 and, as with all these test methods, there are good  
20 and bad points about that procedure.

21 I also wanted to try, I think, to say  
22 something about the nonirritating, which I think we

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1 originally did put in the first publication of the  
2 panel's report.

3 We were looking at that word,  
4 nonirritating -- If you all remember, this is an  
5 ingredient review, and the intention was to focus the  
6 industry and whoever was preparing a product from the  
7 monograph that the formulation should be made so that  
8 it was nonirritating or an attempt should be made.

9 I think we all recognize that with  
10 antimicrobial chemicals we are dealing with somewhat  
11 irritating products and, as Dr. Larson pointed out,  
12 really, no matter what you wash with, if you wash  
13 enough times a day, you're going to have some  
14 irritation to the skin and, certainly, weather  
15 conditions and relative humidity make quite a  
16 difference in what the irritation results are.

17 CHAIRMAN BRASS: Thank you. Dr. Koda-  
18 Kimble?

19 DR. KODA-KIMBLE: I'm feeling like we're  
20 making it complicated again. One of the things that  
21 I feel is complicating is that, when we begin to again  
22 think of the spectrum of use of these agents from

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1     childcare, when you think about antiviral effects, to  
2     food handling and all of that, I wonder if it is  
3     possible to indicate a single standard for antiseptic  
4     use in a high risk situation by taking the most -- not  
5     everything, but the most common organisms that are  
6     likely to be at risk.

7             If somebody wanted to make claims beyond  
8     the usual standard -- because I'm even remembering Dr.  
9     larson's presentation. A nurse is not a nurse is not  
10    a nurse. It depends upon where they're practicing in  
11    the hospital, which patients they're working with,  
12    what organisms they're in contact with.

13            For the public, I think all of us -- and  
14    the public are more highly sensitized to the  
15    possibility of transmission of infection with improper  
16    hygienic techniques and, if the panel could do one  
17    thing, which is to say there are products on the  
18    market that would be useful, potentially useful, in  
19    decreasing transmission of infection, if they are used  
20    in the following way, and particularly in the  
21    following situations.

22            I think that could be very useful. By,

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1 you know, saying in this situation you would do this,  
2 in that situation you would do that, I think it just  
3 makes it ever more confusing.

4 Now I don't know whether that's being too  
5 simple, whether that's impossible, but I would plead  
6 for something simpler than more complicated in this  
7 situation.

8 CHAIRMAN BRASS: Dr. Neill, did you have  
9 another comment?

10 DR. LARSON: Dr. Brass.

11 CHAIRMAN BRASS: Yes, Dr. Larson?

12 DR. LARSON: One other way that might help  
13 us as we grapple with this, because we keep going  
14 between what's a sort of standard level or a minimum  
15 level of safety and efficacy and what's clinical  
16 relevance and what's, you know, the outcome of  
17 infections, is to really take -- and it might be  
18 possible to even tackle it in two steps.

19 One is what does the product need to  
20 demonstrate an acceptable level of safety and  
21 efficacy, and the claim is this demonstrates in a  
22 standard way a level of safety and efficacy.

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1           Then the next level even of label claim,  
2           for example, might be what is the evidence that this  
3           has anything to do with infection.

4           I do think that we've got enough evidence  
5           that there clearly is a dose response and that the  
6           fewer germs you have, the less likely you are to have  
7           an infection. I mean, that's the germ theory again,  
8           but --

9           CHAIRMAN BRASS: I also plead with  
10          Lister, too.

11          DR. LARSON: Yeah. But maybe we should  
12          just tackle those in two separate things. First of  
13          all, what would be a way to say this product meets the  
14          minimum acceptable standard as an antiseptic or  
15          whatever we call it.

16          Then the next is what standard needs to be  
17          met to say that there is actual clinical relevance --

18          CHAIRMAN BRASS: An indication?

19          DR. LARSON: Yes, because whether or not,  
20          for me personally, there's clinical evidence of  
21          reduction of infection, I want to know, first line, is  
22          this product efficacious in a certain way, i.e., does

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1 it reduce the numbers of counts, etcetera, and is it  
2 safe to use. That's necessary.

3 Then the next step would be what's the  
4 impact. The labelling might be in two levels. So  
5 some products might have both claims. Some might have  
6 one, but it seems like that would be another way to  
7 simplify it for us as we address it, too; because we  
8 can't -- Yeah, there are two different related and  
9 important issues.

10 One other comment about flexibility. I'm  
11 the Chair of a hospital infections control practices  
12 advisory committee, HICPAC, for CDC. We struggle with  
13 the same thing.

14 When we promulgate a guideline and it gets  
15 in hard copy in the Federal Register and in journals  
16 and so forth, and then a new study comes out and  
17 something has totally changed in terms of occupational  
18 health or surgical site infection or whatever, what do  
19 we do?

20 The guideline is out there. People are  
21 following it. What we've decided to do from now on is  
22 to say that this is a guideline effective X date, and

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1 updates will be on the Web X number of times a year.

2 We know we still have to go through the  
3 approval -- the usual government approval processes  
4 for changes, but that allows us to have a hard copy  
5 with a caveat that this isn't the end and so forth.

6 Until we can use these new modern methods  
7 of keeping things updated, we're going to have trouble  
8 with these. They're always going to be tentative. So  
9 let's just say they're tentative, effective X date,  
10 with updates coming once a year or whatever.

11 CHAIRMAN BRASS: I think, certainly, as I  
12 have thought about it from our previous discussions,  
13 as Dr. D'Agostino appropriately points out and as you  
14 have as well, Dr. Larson, I've actually come to the  
15 construct you just indicated, that there are two  
16 different things in my mind.

17 Is this an antiseptic agent, and does it  
18 have an indication for use? The categorization is an  
19 attempt to begin to define those indications, but it  
20 is not clear how that relationship between the  
21 indication and that baseline assessment is linked.

22 I think in general -- Coming back to Dr.

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1 D'Agostino's point, I think that -- and paradoxically,  
2 many of these high risk situations -- the event rates  
3 are high enough that there's no question a clinical  
4 trial can and should be done, that there is no need to  
5 initially assume a surrogate, whether it be in vitro  
6 or in vivo, for some of those indications.

7 Again, I don't know how far down the  
8 continuum you want to go to reach that in your initial  
9 assessment, but I think, unambiguously, it is so; and  
10 those same studies can then yield validated surrogates  
11 as opposed to unvalidated surrogates.

12 Right now, again, I think part of the  
13 issue with looking at the data that was presented this  
14 morning of "accepted agents not meeting the standard,"  
15 as was pointed out, there's two explanations for that.  
16 Accepted agent isn't really an acceptable agent for  
17 that indication or standards aren't right.

18 I think the use of appropriate positive  
19 comparators rather than arbitrary levels, with  
20 appropriate statistical power for studies using  
21 positive comparators as opposed to placebo control may  
22 be a way around an arbitrary endpoint that's a

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1 surrogate until validated surrogates can be  
2 identified.

3 In general, when one considers the use of  
4 a surrogate endpoint rather than a definitive  
5 endpoint, the risk/benefit of the outcome matters a  
6 lot, and when both the benefit is low and the risk is  
7 low, then your willingness to accept a surrogate goes  
8 up. That may be where you are for the consumer kinds  
9 of products, but again it seems to me, listening to  
10 the discussion, rather than pretending there is  
11 certainty where there is none that simply allowing the  
12 flexibility and, in my sense, a positive comparator  
13 for what would generally be accepted as a known  
14 antiseptic agent and a non-difference or better than  
15 test.

16 I'll let my statistical colleague comment  
17 on the problems of using positive comparators as  
18 opposed to fixed endpoints or placebo controls, but I  
19 think that might be a formulation to get you out of  
20 this quandary and this box you've built yourself into.

21 DR. LARSON: The irony is that there are  
22 more data demonstrating the effectiveness of hand

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1 hygiene, both with plain soap and some value -- there  
2 are data about some value added in certain risk areas  
3 for antiseptic products than there are for many, many  
4 other things that we -- you know --

5 CHAIRMAN BRASS: Yes. I think that's  
6 really important, because -- and I meant to mention  
7 this earlier. I think it's really dangerous to allow  
8 anecdotal statements substitute for existing high  
9 quality data or potentially high quality data, that no  
10 matter how well characterized the anecdote, it is  
11 still subject to a number of inputs and uncertainties  
12 that allow it to be used as a basis for decision  
13 making, to be no matter than the unvalidated  
14 surrogate, in my opinion.

15 Dr. D'Agostino.

16 DR. D'AGOSTINO: Yes. You had just stated  
17 very much what I was trying to get at in the questions  
18 I was raising. I don't know how we sort of interfere  
19 with the monograph process, and I think there's a lot  
20 of shuddering going on in the audience that what are  
21 you telling us to do; but I mean, I think that I have  
22 not been overwhelmed by the fact that the existing

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1 criteria is too stringent, not because I don't believe  
2 you.

3 I mean, I think that you -- I presume  
4 you're telling me the truth. I just don't have enough  
5 data to sort that out. So I'd say, well, lower it if  
6 you like, but lower it to what? I don't have the  
7 faintest idea why it came up to what it is now in the  
8 discussion.

9 You know, I've been reading this material,  
10 and I've been reading it for only three or four years  
11 as opposed to 25 years, but I still don't get it, and  
12 I don't have access to the particular data that  
13 companies are submitting. So I'm deficient on that,  
14 but certainly, the stuff that we've been seeing. So  
15 I don't know how to move it up and down. But even  
16 more, I don't know why -- I don't find it compelling  
17 on why this plethora of tests are given, and I keep  
18 running to -- My mind keeps saying, well, why don't  
19 you do the clinical trials.

20 I agree 100 percent that it should be a  
21 positive control. You have to be careful when you go  
22 down to population levels and so forth, but some of

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1 these higher levels -- I mean, I don't know -- As I  
2 say, I don't know what interference we're going to get  
3 with the monograph process, but I think very much that  
4 those should be the types of things that we say at the  
5 end of the day here.

6 As far as the positive control trials,  
7 there are a lot of difficulties with positive control  
8 trials, but we're well aware of them. And I'm sure a  
9 lot of these products that are available, in fact, are  
10 useful as a positive control trial.

11 As these trials are run, we'll learn about  
12 them and how they start stacking up and so forth. I  
13 think, you know, I'm not so overwhelmingly concerned  
14 that the interpretation of positive control trial is  
15 going to be anymore difficult here and it's going to  
16 foul up the whole situation.

17 I think that it's going to actually work  
18 out a lot easier than in many other fields where  
19 positive controls start introducing lots of side  
20 effects that you have to really worry about. We don't  
21 seem to have that here. So I think these are going to  
22 actually be fairly smooth trials, but I do think they

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1 are fouling up the process. But I do really feel  
2 compelled to make my recommendations in that direction  
3 and --

4 DR. LARSON: Okay, I agree. So let's take  
5 that another step. I mean, seriously, let's think  
6 about how you would set up a trial. Let's say that  
7 you do it in the classic way so that you randomize.  
8 You have two comparable groups in a hospital, and you  
9 randomize them to one soap versus the other.

10 Then -- I am just foreseeing a problem  
11 here that I think we should anticipate. Let's say  
12 that there is a result which is the result of a  
13 rigorous enough clinical -- randomized clinical trial  
14 that, whether the results are positive or negative,  
15 you can believe them.

16 The next step is, oh, well, that was in a  
17 bone marrow transplant unit with X product. That  
18 doesn't say anything about everything else on the  
19 market. Oh, that was with an alcohol; that doesn't  
20 say anything about CHG. Oh, that was with Triclosan;  
21 that doesn't say anything about pediatric people  
22 using.

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1 So my concern is --

2 DR. D'AGOSTINO: I guess I'm overwhelmed  
3 with that discussion, but I guess I feel so much more  
4 comfortable hearing it happen to bone problems than I  
5 am that it happened in a test tube.

6 I mean, you know, this is what I'm  
7 grappling with, that I would be much more comfortable  
8 with it happening in a couple of different settings  
9 than in no in-use setting, no actual use setting; and  
10 I think that that's part of the question.

11 You have to ask when are we willing to  
12 extrapolate? When are we willing to generalize? I  
13 think that's part of what we have to do.

14 DR. LARSON: Right. But what I'm saying  
15 is I think that still doesn't preclude a two-step  
16 process, one where we have products that meet a  
17 certain standard and another where we look at clinical  
18 relevance.

19 DR. D'AGOSTINO: Yes. I'm sorry, but I  
20 never was implying the removal of what that was being  
21 said. I was going on to these other discussions about  
22 the actual clinical testing.

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1 CHAIRMAN BRASS: And I was also suggesting  
2 that the positive control could be the standard in  
3 vitro testing, too, rather than the arbitrary  
4 standard.

5 I think the issue you raise also gets back  
6 to interpretability. When you start doing the  
7 clinical test as part of the standard, what  
8 formulation changes mean.

9 DR. LARSON: Frankly, I think that's as  
10 much a --

11 CHAIRMAN BRASS: And that's where we go  
12 outside the monograph, and now I'll recognize Dr.  
13 Katz.

14 DR. KATZ: And actually, that's sort of  
15 the key into sort of where I wanted to be, as I'm  
16 listening to this discussion. I just wanted to remind  
17 everyone what we are talking about is really the  
18 monograph process, that this is an ingredient base  
19 process. We're not talking about specific drug or  
20 specific drug product, that this is a broader  
21 spectrum, ingredient based review.

22 So that, if one decides that we would need

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1 clinical trials for what's being discussed here, that  
2 would mean we're talking again final formulations, and  
3 each final formulation would need a clinical trial.

4 DR. LARSON: That's the problem.

5 DR. KATZ: And that's basically why I  
6 wanted to sort of bring us back, because a lot of what  
7 I'm hearing is a very interesting discussion, and  
8 actually I didn't want to stop it. But I wanted to  
9 make sure that everybody knows what realm they're  
10 going toward, to see if that's really where they want  
11 to be, because that may not really answer the  
12 questions that we need to have answered for an  
13 ingredient based drug review, which is where the  
14 monograph comes from, as opposed to a specific drug  
15 based trial.

16 CHAIRMAN BRASS: But is it clear -- Again,  
17 is it clear that formulation doesn't matter, for  
18 example, for characteristics like persistence in a  
19 clinical product, that doesn't formulation matter?

20 DR. KATZ: Formulation does matter, and  
21 actually, it's part of the issues that we're also  
22 trying to find, is in which kinds of formulations does

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1 it matter. Which ones do you need final formulation  
2 testing, and what kind of final formulation testing do  
3 you need.

4 That's where it kind of brings us back to  
5 we all started from, which is that are surrogates  
6 adequate for final formulation testing or do you  
7 really need clinical trials to do final formulation  
8 testing, which is kind of again going round about to  
9 where we started from earlier.

10 DR. D'AGOSTINO: I'm still -- I'm not sure  
11 I -- I've been with the OTC review for about 25 years  
12 in different capacities of consulting and so forth.  
13 So this is what I meant when I was saying how it's  
14 going to impact on the monograph process.

15 I just don't understand the problem you  
16 raised as somehow or other saying, okay, then great,  
17 let's get rid of clinical trials. I mean, it leaves  
18 me even worse that, you know, I --

19 DR. KATZ: I never said that. What I  
20 basically said is that when you're thinking about what  
21 you're going ahead to recommend, remember that, being  
22 that this is an ingredient based review as opposed to

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1 a specific drug, whatever you propose is going to have  
2 to go through the whole spectrum.

3 So if what the committee comes down and  
4 says now is that clinical testing is needed, well,  
5 that's fine. That may be something that we'll  
6 address, but I just want to make sure everybody  
7 understands what process they're going through.

8 We're not talking the NDA process. We're  
9 talking a monograph.

10 CHAIRMAN BRASS: Yes. And I think Dr.  
11 D'Agostino understands that. I know I understand  
12 that, and I think what we're trying to convey is that  
13 in going from the idealized even clinical trial to  
14 developing a monograph based on surrogates, the dotted  
15 line at least has to be visible in a somewhat linear  
16 way and not a curlicue with huge gaps in it.

17 I think that's what we're seeing going  
18 from what we have now to the monograph in how those  
19 surrogates have been formulated.

20 Other comments from the panel? Are there  
21 from the agency's perspective in our free floating  
22 angst that we have not addressed for you yet?

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1 Dr. D'Agostino?

2 DR. D'AGOSTINO: Can I ask what would be -  
3 - not from the agency, but from maybe Dr. Larson --  
4 What would be, for example, a nice outcome of this  
5 meeting to recommendations for the FDA? I mean, I  
6 hear the two-tiered bit, and I'm 100 percent behind  
7 it.

8 I've expressed my concern about the lack  
9 of clinical trials. There are settings with clinical  
10 trials I use and so forth, and those are sometimes  
11 reasonable, sometimes not. You've given the  
12 experience you've had, for example, for 25 years or  
13 what have you.

14 What would be, you think, a reasonable set  
15 of statements to make to the FDA?

16 DR. LARSON: Well, actually, we probably  
17 said some actually useful things today, and --

18 CHAIRMAN BRASS: Even if by accident.

19 DR. LARSON: I think, if we agree that we  
20 would like to see as much as possible the test set up  
21 in a way that is clinically meaningful, that's  
22 something that would be helpful.

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1           If we agreed that there could be the  
2           potential for a two-tiered idea so that the claim has  
3           nothing to do with infection unless there are clinical  
4           trials, but that we could still have a standard that  
5           got decided on without having this be -- It seems like  
6           this is what always holds us up from moving it  
7           forward.

8           So if we could be real clear in that, and  
9           then if we could find a way to allow for fairly  
10          expeditious modifications to the monograph in real  
11          time, i.e., less than a decade between -- in other  
12          words, figure out a way, as new information comes  
13          along, to make modifications. Those would be three  
14          great steps forward.

15          I think that the current one is a vast  
16          improvement over the first one, and we always like to  
17          be hard on the agency. I think it's an improvement.  
18          I think there is openness, but there seems to be a  
19          level of inability to just decide to go ahead and set  
20          up some standards that are reasonable.

21               CHAIRMAN BRASS: I would add to kind of  
22          this compiling list of things that there seem to be

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1 emerging consensus about the need for flexibility and  
2 not having the monograph constructed in a way that  
3 prevents innovative ways of demonstrating the same  
4 objective by the industry.

5 Yes, Dr. Leyden?

6 DR. LEYDEN; Jim Leyden, University of  
7 Pennsylvania.

8 Just to follow up what Elaine was saying  
9 and somewhat of what I said earlier this morning is  
10 that we do have 25 years of experience. We have had  
11 proposals and improved proposals, and I think the  
12 major thrust of this morning was that some of the  
13 proposals now have technical issues that, as Elaine  
14 said, could be easily handled.

15 Now many of you have expressed the  
16 appropriate point of view that whatever test you do  
17 ought to mean something. Okay. Now we have an  
18 enormous experience with several compounds,  
19 particularly chlorhexidine, povidone iodine and, more  
20 recently, with Triclosan, PCMX and a few others.

21 We have a lot of clinical experiences.  
22 You heard Dennis this morning talk about reducing the

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1 rate of infection, and his point of view was that one  
2 agent was far superior to the other, but the other was  
3 effective.

4 So we do have experience that these things  
5 do something that means something. We can't go out  
6 and do a clinical trial of, you know, people washing  
7 their hands at home, because we have to select  
8 populations and show that something happens.

9 We have a study that was done at enormous  
10 expense that shows that you can make a difference in  
11 atopic eczema with a modest reduction in bacteria. It  
12 had a clinical reduction

13 We have a lot of data that, I think, a  
14 reasonable group of people, some from the FDA. Some  
15 people have been doing this kind of thing as a  
16 research enterprise for some years, can get together  
17 and look at the data and say this is our best analysis  
18 in 1998.

19 As Elaine says, if we need to change it  
20 next year, let's have a mechanism so we can change it,  
21 instead of having these meetings and then we come back  
22 in another two years and we have the same meeting, and

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1 we come back in another two years and we have the same  
2 meeting.

3 CHAIRMAN BRASS: Well, I think what the  
4 panel is struggling with is how to take that database  
5 that does exist and integrate it into the rulemaking  
6 process in a constructive way, so that, for example,  
7 if we take the two-tier approach, the agents you have  
8 identified would all be antiseptic agents using a  
9 variety of criteria, and we could agree on that.

10 Let's take your example of an agent that  
11 was proven efficacious on some clinical endpoint for  
12 atopic dermatitis. How does that extrapolate to every  
13 American taking a bath in it every night?

14 DR. LEYDEN: Well, it only extrapolates to  
15 them if they have atopic eczema, which --

16 CHAIRMAN BRASS: That's our point.

17 DR. LEYDEN: -- about 15 percent of people  
18 have.

19 DR. LARSON: See, that could be the second  
20 tier for that application --

21 CHAIRMAN BRASS: Exactly. That's what  
22 we're trying to specify.

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1 DR. LARSON: -- only, and then that  
2 product can make the claim for that application, if  
3 it's a rigorous, you know, randomized clinical trial,  
4 whatever, and then it could have a second tiered claim  
5 for that.

6 DR. LEYDEN: But if the agency -- If the  
7 FDA says, okay, here are our people, you know, people  
8 from the food, people from the anti-infective  
9 division, whatever -- these are the people we think  
10 should be involved in this distillation of what  
11 information we have, here are the people from  
12 industry, here are the other people; get in a room,  
13 and don't come out until you have an agreement, you  
14 know.

15 Come to an agreement, and then report it  
16 back to a panel like this or to whoever, and  
17 disseminate it in the Federal Register and let people  
18 comment on it, and then make a decision and say this  
19 is what we're going to do, and this is the mechanism  
20 to add modifications as modifications become.

21 Otherwise, we'll be here in ten years,  
22 Elaine, and we'll be showing the same slides and

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1 saying the same things.

2 CHAIRMAN BRASS: Do you have additional  
3 comments, Dr. D'Agostino?

4 DR. D'AGOSTINO: No, no. I'm quite in  
5 agreement with this discussion.

6 CHAIRMAN BRASS: Dr. Neill? Dr. Katz, you  
7 wanted to --

8 DR. KATZ: I just wanted to make one sort  
9 of brief aside, is that the current actual indications  
10 that are proposed are actually fairly general. Part  
11 of the reason why they are so general is so that they  
12 would go -- they would encompass a broad spectrum of  
13 individuals who might actually use the products.

14 So that's currently the way it's done  
15 right now, just again so that way that something would  
16 not be so product specific that we couldn't  
17 extrapolate to somebody else.

18 CHAIRMAN BRASS: Dr. Neill?

19 DR. NEILL: I'm going to try and answer  
20 the questions that you posed to us in that note here,  
21 because I think that our role -- I think our role as  
22 an advisory committee is to offer --

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1 CHAIRMAN BRASS: This is your first  
2 meeting. We try not to follow the directions.

3 DR. NEILL: It is. Oh, okay. This then  
4 is a comment on my suitability, I'll let my comment  
5 stand on its own.

6 You're asking in general terms what are  
7 the appropriate tests to reach the performance  
8 characteristics. What I've heard is a large minority  
9 or even majority -- minority -- of people recommending  
10 that clinical trials may be the most appropriate,  
11 given the caveat that there are already mechanisms in  
12 place to allow for clinical trials to relate to  
13 specific additional or tier-two indications or even  
14 through the NDA process to get products on the market.

15 Short of that, I think the criteria that  
16 were laid out by you with some modifications by  
17 industry seem appropriate. Specifically, in terms of  
18 persistence there seems to be a disagreement between  
19 the very explicit set of testing that you lay out in  
20 this proposal and the desire to include ASTM tests for  
21 persistence on the part of industry.

22 I'm not sure how those tests disagree, how

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1     you're -- you may have drawn specifically from ASTM.  
2     I think you make some reference in some of the product  
3     persistence tests to ASTM mechanisms, but that seems  
4     to me to be the type of disagreement that is the --  
5     you know, ten second versus 15 second, and the thing  
6     that people smarter than me are going to have to  
7     haggle with and who have a longer life expectancy.

8             In terms of onset, it seems like there's  
9     some agreement about using ASTM. In terms of spectrum  
10    of antimicrobial action, it seems like both agree on  
11    using some version of MIC.

12            In terms of activity against resistant  
13    versus transient bacteria, some combination of MIC and  
14    time kill data; and while there's disagreement about  
15    an actual endpoint versus a log reduction and maybe  
16    disagreement about the exact starting setting, the  
17    methods seem to be in agreement.

18            One thing that is -- was commented on  
19    briefly earlier today, but that concerns me slightly,  
20    is that there's not much disagreement about measuring  
21    the potential for irritation, because while you  
22    propose some standards for measuring this, there

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1 doesn't seem to be in the industry proposal, as I  
2 could figure, as specific a way to measure that.  
3 Maybe that's just because I'm a bad reader.

4 The reason that raises a question in my  
5 mind is because I'm -- I think I was, you know, ten or  
6 12 when pHisoHex was all over the place, and that's  
7 what I was supposed to use for my acne, etcetera, and  
8 now it doesn't exist, but I'm not sure why.

9 I believe that that's related to why we're  
10 sitting here today, and I'm unfamiliar with the  
11 processes that are in place, either FDA or industry,  
12 to monitor or provide surveillance data for things  
13 like irritation, side effects, etcetera.

14 I don't know. That's not really a  
15 question. Let me put it in the form of a question.  
16 No, let me try and get back to answering your  
17 question.

18 I do think it's important to have  
19 criteria, a testing criteria that can be stated,  
20 whether it's animal based or theory based, model  
21 based, whatever, to define what constitutes acceptable  
22 levels of irritation, and I think that there ought to

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1 be some sort of agreement about a surveillance system  
2 in place, specifically, rather than we'll let the  
3 market decide.

4 Your second question, should testing  
5 requirements be based on intended use? Yes. If so,  
6 how? It's pretty clear, we don't know.

7 CHAIRMAN BRASS: Would other radicals like  
8 to comment on the specific discussion points?

9 DR. D'AGOSTINO: A breach of protocol.

10 CHAIRMAN BRASS: Other comments from  
11 anybody? Please? Please identify yourself for the  
12 transcriptionist.

13 DR. SATTAR: I am Syed Sattar from the  
14 University of Ottawa in Canada.

15 Mr. Chairman, my personal view is that  
16 even the in vitro testing as specified in the existing  
17 version of TFM is perhaps unreasonably stringent or  
18 demanding, in the sense that it requires too many  
19 strains of bacteria to be tested.

20 I feel that it is totally uncalled for,  
21 because the answer that you will get will really not  
22 increase the level of confidence in the end result in

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1 terms of the testing itself.

2 The concept of using surrogates in terms  
3 of microorganisms for testing -- this has now become  
4 a fairly accepted practice. If you look at what the  
5 other part of FDA does when they deal with high level  
6 disinfectants, they use surrogates, one type of  
7 mycobacterium of two type of mycobacteria, two types  
8 of bacteria spore, and they base their evaluation on  
9 the performance of those products as to their activity  
10 against the surrogate.

11 Even in the EPA, when they look at  
12 household disinfectants, the concept of surrogates has  
13 become a part of the regulatory evaluation process.

14 So I feel that there are too many bacteria  
15 that are required to be tested, and I can't resist the  
16 temptation of feeling that the requirements for those  
17 many bacteria actually come from an antibiotic  
18 mindset, not from a germicide mindset.

19 I think we should be sensitized to that  
20 fact.

21 CHAIRMAN BRASS: Other comments?

22 Questions?

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1 Well, if not, I'd like to thank very much  
2 all the participants for their stimulating and on time  
3 discussions, all our discussants, and the panel  
4 members, very much.

5 We are adjourned.

6 (Whereupon, the foregoing matter went off  
7 the record at 3:17 p.m.)

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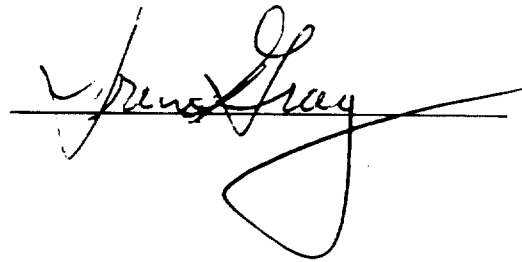
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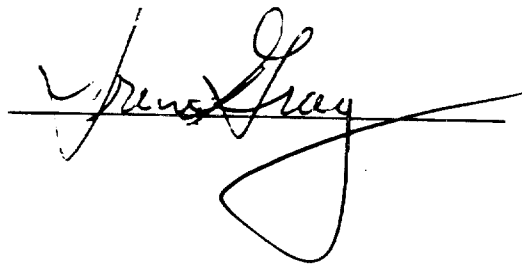
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